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Preparation and In-Vitro Evaluation of Donepezil Hydrochloride Sustained Release Matrix Tablets Using Non-Gelling Polymer

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Abstract: *The aim of the current investigation was to develop a Sustained release tablet of Donepezil Hydrochloride using non- gelling polymer in order to overcome the problem of dose dumping. Viscarin GP-209 was used as a non-gelling release modifying agent. The formulated granule blends were evaluated for powder properties. Prepared tablets were subjected to post compression evaluations. In-vitro dissolution studies were carried out in 3 different dissolution profiles. Profile1: 0.1 N Hcl medium, Profile 2: pH 5.5 sodium phosphate buffer medium and Profile3: in 0.1 N Hcl for 2hrs and in 6.8 pH sodium phosphate buffer medium using the USP Type 2 apparatus as per the FDA guidelines. The dissolution data was fitted into various kinetic models to determine the release mechanism and mean dissolution time. Formulation F6 was considered as optimized as it showed similar drug release pattern with that of innovator immediate release formulation and similarity factor (f2) of 82. F6 formulation was found to be stable up to 3 months of stability testing at 40^{o}c / 75%RH.*

Key Words: *Donepezil hydrochloride, similarity factor (f2), sustained release, Viscarin GP - 209.*

I. Introduction

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of Sustained drug delivery, greater attention is being paid on development of oral sustained release drug delivery systems. The goal in designing sustained release drug delivery system is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, Sustained release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ [1-3]. Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Sustained release preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time usually 8-12 hrs [1].

Donepezil Hydrochloride (DH) is a second-generation cholinesterase inhibitor (ChEI), used for the treatment of Alziemers disease (AD) having greater specificity for the brain acetyl cholinesterase enzyme (AchE). This compound characterized by a long plasma half-life (70h) and a bioavailability of 100%[2]. Initially DH was available in immediate release dosage forms, which resulted in spikes in the patient's blood plasma levels within 2 to 5 hrs after the drug administration[3]. Eisai Research Institute discloses a sustained release formulation of Donepezil Hydrochloride that overcomes the side effects of the immediate release formulations[4].

Designing a sustained release formulation of water soluble active agents and their pharmaceutically acceptable salts, using a gelling agent would be very difficult. The gelling agent forms a gel in contact with water. Such kind of composition is susceptible to a phenomenon known as dose dumping. That is, release of the active ingredient is delayed for a time but once release begins, the rate of release would be very high. Moreover, fluctuations tend to occur in the plasma concentrations of the active ingredient which increase the likelihood of toxicity[5].

Carrageenan is generally used in the oral solid dosage forms such as in tablet formulations to impart release characteristics. Carrageenan being hydrophilic absorbs water from surroundings when placed in aqueous liquids and there by forming a viscous gel, this gel in turn slows down the release of active ingredients embedded in it and provides a sustained release of the drug from the formulation. Unlike all the grades of carrageenan, λ- carrageenan (Marketed under the trade name Viscarin GP) is a hydrophilic agent which shows no gelling properties upon absorption of water from surroundings when placed in aqueous liquids. Such kind of grade of carrageenan can still impart sustained release properties to a solid oral dosage form such as tablet [5]. Thus, a need exists in the art for a simpler design of sustained release formulations of soluble medicaments such as DH using non gelling polymer, λ- carrageenan by conventional manufacturing procedures.

II. Materials And Methods

1.1 Materials:

Donepezil hydrochloride was supplied as a gift sample from Dabur Research Foundation, Ghaziabad, India. Lambda carragennan was purchased from FMC Biopolymer, Mumbai, India. Lactose Monohydrate, Microcrystalline cellulose, PVP K-30, Dichloromethane, Magnesium stearate were purchased from SD Fine-Chem. Pvt., Mumbai, India.

1.2 Analytical method development

1.2.1 Determination of λ-max

10 µg/ml standard solution of Donepezil hydrochloride in purified water was scanned on a double beam UV spectrophotometer. From the UV spectrum of Donepezil hydrochloride λmax was obtained.

1.3 Drug – Excipients compatibility study:

1.3.1 FTIR studies:

The compatibility between Donepezil Hydrochloride, λ- carragennan, Lactose monohydrate, microcrystalline cellulose, PVP K-30, Dichloromethane, and Magnesium stearate was detected by FTIR spectra obtained from Bruker FTIR Germany (Alpha T). Potassium bromide pellets were prepared on KBr press. Powder sample and KBR were ground together in a mortar in 1:100 ratios. The finely grounded powder was introduced into a stainless steel die. The powder was pressed in the die between steel anvils at a pressure of about $10t/in^2$. The spectra's were recorded over the wave number of 8000^{-1} to 500 cm^{-1}.

1.4 Preparation of Donepezil Hcl Sustained Release tablets

Wet granulation method: Composition of various tablet formulations is listed in Table: 1. Donepezil hydrochloride (DH) sustained release tablets were prepared by wet granulation technique. All the ingredients were weighed and passed through sieve no, 40 separately. The Intragranular mixture was prepared by mixing Donepezil HCL, lactose, microcrystalline cellulose and λ- carragennan. Binder solution was prepared by mixing PVP- K- 30 in dichloromethane. To the Intragranular powder blend binder solution was added to prepare a uniform mass. The wet mass was screened through sieve to obtain granules. The granules were dried at room temperature. The dried granules were again passed through sieve no. 22 and were lubricated with an extra granular mixture. Finally, the lubricated granules were compressed into tablets with an average weight of 200mg using 8 mm concave punches in an eight station rotary tablet press (Riddhi, Ahmadabad, India) to a hardness of 4-5 kg/cm^2.

Table: 1: Composition of various tablet formulations:

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Intragranular						
Donepezil Hcl	23	23	23	23	23	23
Lambda carragennan	63	48	53	38	53	38
Lactose monohydrate	72	87	82	97	77	92
Microcrystalline cellulose	5	5	5	5	5	5
PVP-K 30	5	5	5	5	10	10
Dichloromethane	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular						
Magnesium stearate	2	2	2	2	2	2
Lambda carragennan	30	30	30	30	30	30
Total weight	200	200	200	200	200	200

1.5 Evaluation and characterization :

2.5.1 Evaluation of granule properties

2.5.1.1 Angle of repose: [6]

Repos graph was used to measure the angle of repose. The apparatus consisted of mini-hopper with a base platform, which is divided into zones. The mini-hopper was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. The cone formed on the base was examined to observe the zone, thereby evaluating the flow ability of the granules. It can be calculated using the formula,

$$\tan \theta = h/r$$

Where, h = Height, r = Radius, θ = Angle of repose.

2.5.1.2 Bulk Density: [7]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 gm of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own

weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was observed. LBD and TBD were calculated using the following formula:

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}$$

2.5.1.3 Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr`s index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

2.5.2 Evaluation of Tablets: [8, 9]

2.5.2.1 Thickness:

The thickness in millimetres (mm) was measured individually for 10 pre weighed tablets by using a digital screw guage.

2.5.2.2 Hardness:

It was determined by placing the tablet between the anvils, only one of which is movable, force is applied till the tablet breaks. Hardness of 10 tablets determined and average hardness and range was calculated.

2.5.2.3 Friability:

Friability of the formulated tablets was determined in Lab India FT 1020. Ten tablets were weighed accurately and then initial weight was note down. These are introduced in the apparatus and subjected to 100 revolutions at a speed of 25 rpm. When the drum stopped, tablets were taken and dedusted and final weight was taken. % friability was calculated by the formula

$$\% \text{ Friability} = \frac{\text{Initial weight (gm)} - \text{Final weight (gm)}}{\text{Initial weight (gm)}} \times 100$$

2.5.2.4 Weight variation:

Weight variation test was performed according to IP. Average weight of twenty tablets was calculated and individual weight of each tablet was taken. % deviation was calculated with respect to average weight. The maximum % deviation allowed is 7.5% as the tablet weight is between 130- 324 mg.

2.5.2.5 Content uniformity:

At random, 20 tablets were weighed and powdered. A quantity of the powder equivalent to 100 mg was transferred into 100 ml volumetric flask containing distilled water and sonicated for five minutes. Volume was adjusted to 100 ml with water and filtered through Whatman filter paper and then diluted appropriately and the drug was estimated at λmax of 230 nm using UV spectroscopy.

2.5.2.6 *In-vitro* release study of prototype formulation:

Dissolution was done for each batch of sustained release tablets in three different profiles for 14 Hrs according to the FDA guidelines[10].

Table: 2: Various Dissolution Profiles

Dissolution conditions	**PROFILE 1**	**PROFILE 2**	**PROFILE 3**
Dissolution Media	0.1 N Hcl medium	pH 5.5 sodium phosphate buffer medium	0.1 N Hcl medium for 120 minutes, then in 6.8pH sodium phosphate buffer medium for 12 hrs.
Apparatus	USP TYPE 2	USP TYPE 2	USP TYPE 2
Volume	900 ml	900 ml	900 ml
RPM	50	50	25
Temperature	37 + 0.5° C	37 + 0.5° C	37 + 0.5° C

2.5.2.7 Study of release kinetics:

The dissolution data was fitted into various kinetic models to determine the release mechanisms. Different kinetic equations (zero order, First order, and Higuchi's equations) were applied to interpret the release rate of the drug from the matrix system[11]. For prediction of mechanism of drug release through

polymeric system Korsmeyer and Peppas, developed a mathematical equation, relating exponentially the drug released to the elapsed time. It is a simple semi empirical equation also called as *Power law*[12].

$$M_t/M_\infty = Kt^n$$

Where, M_t / M_∞ is the fraction of drug released at time 't' and infinite time, 'k' is the kinetic constant, n is the drug release exponent, indicative of the mechanism of drug release.

Exponent, n			Drug Release Mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Anomalous Transport
1.0	0.89	0.85	Case II transport

Mean dissolution time (MDT) is used to characterize the drug release rate from the dosage form and retarding efficiency of the polymer. MDT was calculated using the equation:

$$MDT = n / (n+1) * k^{-1/n}$$

Where 'n' is the release component and 'k' is the kinetic constant calculated from the power law

2.5.2.8 Release Profile Comparision

Similarity factor, f2 value:

The similarity factor *f*2 as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products**:**

$$f2 = 50 * \log\left\{\left[1 + \left(1/n\right)\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5} * 100\right\}$$

Where, n is the number of dissolution time points, R_t and T_t are the reference and test dissolution values (mean of at least 12 dosage units) at time t.

When the two dissolution profiles are identical, *f*2 = 50 * log (100) = 100, and when the dissolution of one product (test or reference) is completed before the other begins, *f2* = 50 * log {(1 + 1/n Σ (100) ^{2})$^{-0.5}$ * 100} = -0.001, which can be rounded to 0. Thus the value of *f*2 ranges from 0 to 100. Two dissolution profiles are considered 'similar' when the f2 value is between 50 and 100. Thus FDA recognizes the profiles to be similar when the two drug profiles differ only by a difference of 10%. A higher f2 value indicates closeness between the two dissolution profiles.

b. Difference factor (f_1):

f_1 measures the percent error between two curves over all time points.

$$f_1 = \frac{\sum_{j-1}^{n}|R_j - T_j|}{\sum_{j-1}^{n} R_j} \times 100$$

Where, *n* is the sampling number, *R* and *T* are the % dissolved of reference & test products at each time point *j*.

The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. It is generally accepted that values of f1 between 0- 15 do not indicate dissimilarity

2.5.2.9 Stability studies: [13]

Optimized F6 formulation was packed in screw capped high density polyethylene container and was isothermally stressed to study the stability under accelerated temperature and relative humidity conditions 40^{o}c and 75% RH in stability chamber for 3 months. Test samples were withdrawn every month and were subjected to various tests, including visual inspection of any appreciable changes of the surface of the tablet, assay, hardness, friability and dissolution.

III. Results And Discussion:

3.1. Analytical development

3.1.1. Determination of λ- max

Donepezil hydrochloride solution was prepared in water and scanned using UV-Spectrophotometer in the range of 400 – 200nm to determine the λ max. The λ max of Donepezil hydrochloride was found to be at 220 nm.

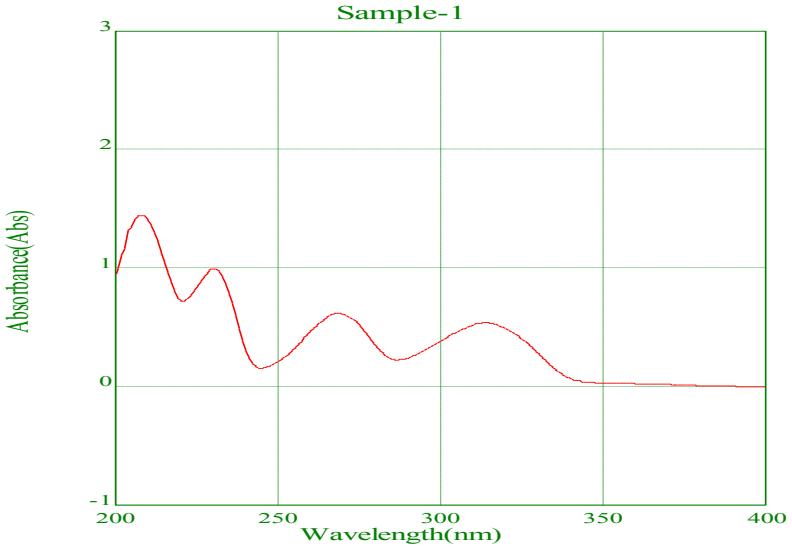

Figure 1: lambda max of Donepezil hydrochloride in purified water

3.2. Drug excipients computability

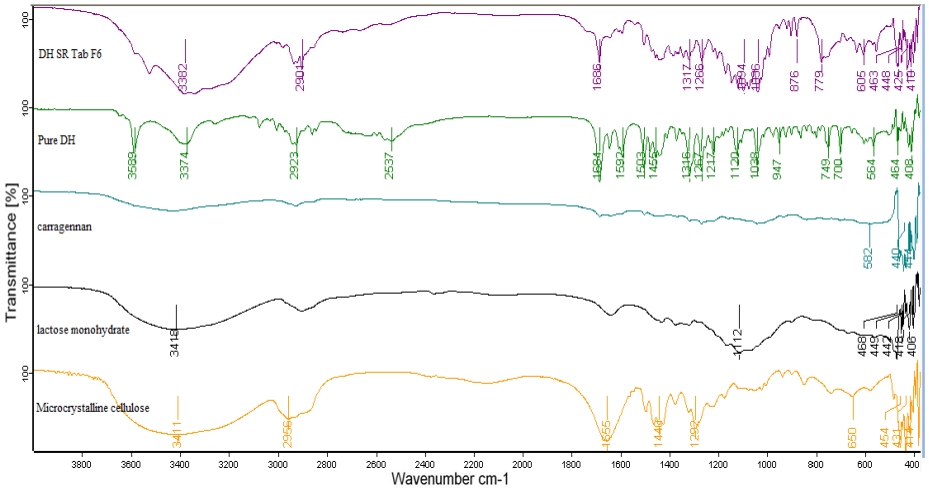

Figure 2: FTIR Spectrum of Donepezil Hydrochloride and Physical Mixture of Drug-Excipients

The FTIR spectra of pure drug and blend of F6 sustained release matrix tablet are shown in Fig.1. From this it is clear that the characteristic peaks at 1684, 1266, 1034 (C=O stretching), 749 (aromatic C-H stretching), 1317 (C-N stretching) cm^{-1} are present in both the pure drug and its formulation containing sustained release polymer matrices, without any change in their positions, indicating no chemical interaction between drug and excipients

3.3. Evaluation Of Granule Properties:

Pre- compression parameters results are tabulated in Table no. 3. Donepezil hydrochloride powder and the prepared granules were evaluated for powder properties. Angle of repose value of prepared granules ranged from 20.46°± 0.03 to 23.98°± 0.03 Furthermore, HR measured for Donepezil hydrochloride powder was 1.428, indicating cohesiveness of the powder and, consequently, the very poor flow ability. HR values of the prepared granules ranged from 1.15 to 1.25. This indicates good flow properties of the prepared granules as a result of increasing particle size owing to granulation. Also, the granulation lowered the tapped density as a result of a relative increase in particle size compared with untreated powder. Tapped density values of the prepared granules

ranged from 0.038 ± 0.08 to 0.41 ± 0.03. Carr's index of Donepezil Hydrochloride powder was 30; whereas the values of the prepared granules ranged from 13.34 ± 0.07 to 20.01 ± 0.07 supporting that granulation improved flow ability and compressibility.

Table: 3: Granule Properties of F1, F2, F3, F4 F5, F6 Formulation (N=3)

Formulation code	Angle of repose (^{0})	Loose bulk density (gm/cm^3)	Tapped bulk density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	21.91 ± 0.02	0.333 ± 0.04	0.416 ± 0.05	20.01± 0.07	1.25
F2	22.28 ± 0.02	0.322 ± 0.02	0.416 ± 0.07	17.25 ± 0.06	1.20
F3	21.36 ± 0.03	0.344 ± 0.04	0.40 ± 0.04	13.80 ± 0.05	1.16
F4	20.46 ± 0.03	0.344 ± 0.04	0.416 ± 0.02	17.25 ± 0.06	1.209
F5	22.81± 0.01	0.32 ± 0.02	0.410 ± 0.03	19.50 ± 0.06	1.242
F6	23.98 ± 0.03	0.33 ± 0.02	0.380 ± 0.08	13.34 ± 0.07	1.154

3.4. Evaluation Of Tablets:

Post- compression parameters results are tabulated in Table no. 4. The physical properties of the prepared tablets were studied by determining average weight, thickness, drug content, hardness and friability. The thickness of the prepared tablets ranged from 4.03 ± 0.12 mm to 4.20 ± 0.02 mm. The friability of the prepared tablet was in the range of 0.41 ± 0.07 to 0.48 ± 0.01 %. Hardness of the prepared tablets was in the range of 4.12 ± 0.38 to 4.82 ± 0.16. The average drug content of the prepared tablet formulation ranged from 95.61± 1.1 to 101.2 ± 1.4.

Table: 4: Tablet Properties of F1, F2, F3, F4, F5 and F6 Formulation

Formulation code	Weight variation (mg), (n=20)	Thickness (mm), (n=10)	Friability (%), (n= 6)	Hardness (Kg/cm^2), (n=6)	Drug content, (n=5)
F1	0.2223 ±0.004	4.037 ± 0.12	0.41 ± 0.07	4.28 ± 0.14	95.61 ± 1.1
F2	0.2015 ± 0.008	4.128 ± 0.08	0.44 ± 0.01	4.12 ± 0.38	98.98 ±1.6
F3	0.2018 ± 0.004	4.076 ± 0.11	0.43 ± 0.02	4.18 ± 0.28	101.2 ± 1.4
F4	0.2005 ± 0.008	4.028 ± 0.09	0.42 ±0.04	4.41 ± 0.16	99.42 ± 1.2
F5	0.1989 ± 0.009	4.186 ± 0.02	0.45 ±0.04	4.68 ± 0.23	99.26 ± 1.6
F6	0.2016 ± 0.004	4.208 ± 0.02	0.48 ±0.01	4.82 ± 0.16	99.94 ± 1.1

The release studies were performed in perfect sink coditions. 94% of drug release from formulation F6 was observved in 0.1N Hcl, whereas 85% release was observed in 6.8pH phpsphate buffer. A significant amount of drug was released in 0.1N Hcl medium compared with that released in 6.8pH phpsphate buffer. 96% of drug release was observed in dissolution medium in contaoning both 0.1N Hcl and 6.8pH phosphate buffer wer used. Thus, it can be concluded that *in vitro* release of donepezil hydrochloride is a direct function of its solubility in the dissolution medium.

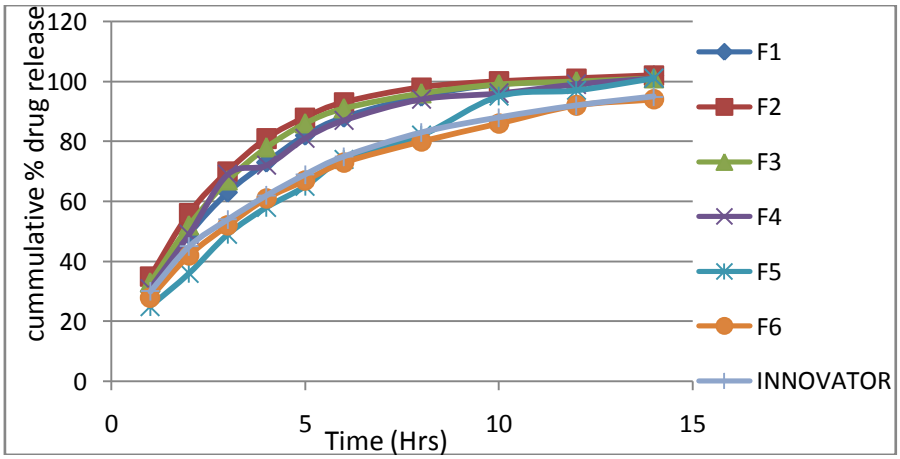

Figure 3: Cumulative Drug Release of F1, F2, F3, F4, F5, F6 and Innovator Formulation in Dissolution

Profile 1

Cumulative percentage drug release of all the formulations were compared with the innovator formulation and it was observed that 'F6' formulation has 94% drug release at the end of 14th hour.

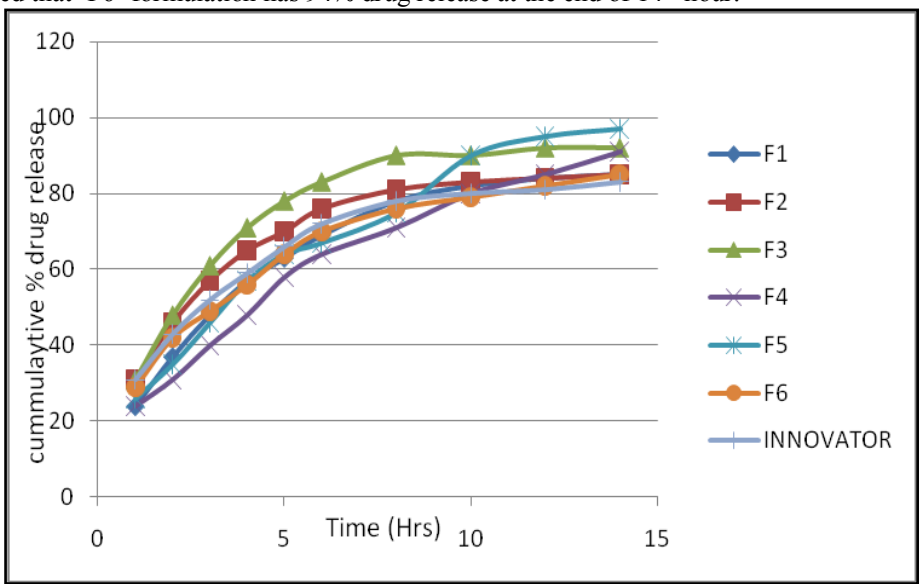

Figure 4: Cumulative Drug Release of F1, F2, F3, F4, F5, F6 and Innovator Formulation Profile 2

Cumulative percentage drug release of all the formulations were compared with the innovator formulation and it was observed that 'F6' formulation has 85% drug release at the end of 14th hour.

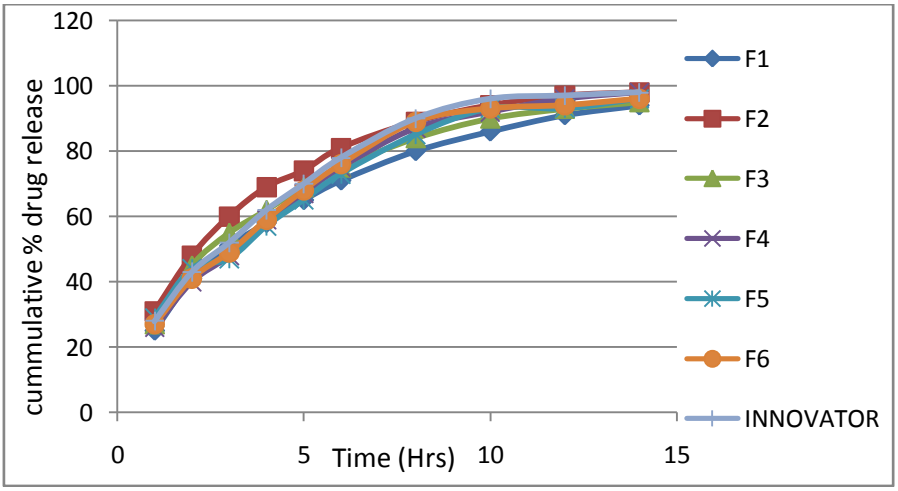

Figure 5: Cumulative Drug Release of F1, F2, F3, F4, F5, F6 and Innovator Formulation Profile 3

Cumulative percentage drug release of all the formulations were compared with the innovator formulation and it was observed that 'F6' formulation has 96% drug release at the end of 14th hour.

3.5. Release Kinetics

Table: 5: Results of Release Kinetics

FORMULATION	ZERO ORDER	FIRST ORDER	HIGUCHI	HIXSON-CROWELL	KORSEMER- PEPPAS		MDT
	R^2	R^2	R^2	R^2	R^2	n	Min
F6	0.858	-0.171	0.992	0.9871	0.8586	0.0022	178.7

As observed from the Table 5, the best fit model with higher coorelation was found with Higuchi's equation for all the formulations. The release exponent 'n' calculated from the peppas chart was found to be(n < 0.5) indicating fickkan (Case I) diffusion mediated release. The Mean dissolution time(MDT) is used to characterize the drug release rate from the dosage form and retarding efficancy of the polymer . The MDT value of the optimized formulation F6 was found to be higher than the other formulations.

3.6. Invitro-Invivo Corelation:

Difference Factor (F1) = 3.08
(0-15)

Similarity Factor (F2) = 81.49
(50-100)

Sustained release matrix tablets prepared using λ-carrageenan are similar to the marketed tablet formulation according to the model independent FDA guidelines (f2 factor).Formulation F6 was seemed to be close to the innovator's release profile. The calculated similarity factor f2 was 82, so formulation F6 has similar release profile to the marketed formulation release. The dissolution profile of optimized formulation was assessed for the release mechanism. The best linearity was found in Higuchi's equation plot indicating the release of drug from a matrix as a square root of time dependent process based on anomalous (non-Fickian diffusion).

3.7. Stability Study:

Table: 6: Stability Studies Results for the Optimised F6 Formulation

Parameter	Initial	1 MONTH	2 MONTH	3 MONTH
Thickness (mm) (n=10)	4.208 ± 0.02	4. 191 ± 0.01	4. 185 ± 0.01	4. 181 ± 0.01
Hardness (Kg/cm^2) (n=6)	4.82 ± 0.16	4.66 ± 0.11	4.59 ± 0.11	4.54 ± 0.11
Friability (%) (n=6)	0.48 ± 0.01	0.43 ± 0.02	0.41 ± 0.02	0.40 ± 0.02
Drug content (%) (n=5)	99.94 ± 1.1	98.08 ± 0.9	97.78 ± 0.7	97.23 ± 0.9

The stability studies of the optimized F6 formulation indicate that the developed SR tablets were unaffected after 3 months storage. The drug content and friability were comparable with those of the control samples and were within limits. On the basis of these results, it is concluded that the formulation F6 is stable under accelerated conditions for 3 months.

IV. Conclusion:

It can be concluded that Donepezil Hcl can be formulated as a Sustained Release matrix tablet using λ – carragennan. The optimized formulation F6 showed cumulative release of 94% drug release at the end of 14th hour in dissolution profile 1, 85% drug release at the end of 14th hour in dissolution Profile 2 and 96% drug release at the end of 14th hour in dissolution profile 3. The drug release from the matrix tablets containing λ – carragennan was Fickian obeying Zero order Kinetics. Stability studies showed that there was no significant change in drug content and *in - vitro* drug release of optimised formulation (F6). The formulation has similarity factor of 82.

Further, in- vivo investigations are required to correlate with in – vitro dissolution studies for the development of optimum oral sustained release matrix tablets of Donepezil HCl.

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