



IN-VITRO EVALUATION OF CO-EXCIPIENTS FOR RELEASE OF DONEPEZIL HYDROCHLORIDE FROM CARBOPOL 974P BASED TABLETS

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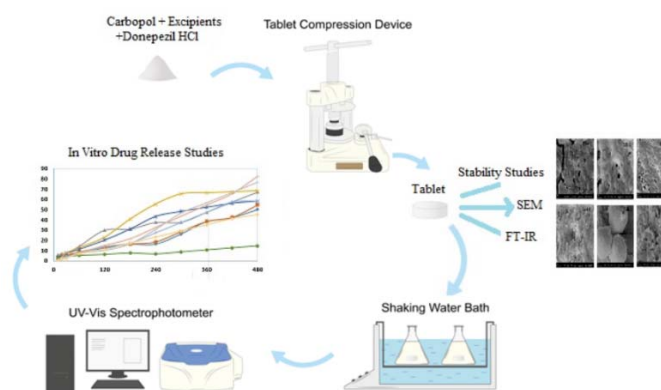
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The prime aims of the present work at formulating and preparing matrix tablets using Carbopol 974P to sustain the release of donepezil HCl. Tablets were prepared by direct compression method and evaluated for the effects of ingredients on the *in-vitro* release behavior. Gelatin, α -cellulose, sodium alginate, hydroxyapatite, and natural zeolite (clinoptilolite) were used as co-excipients to modulate the formulations. The prepared tablets of the 10 formulations were characterized by using Fourier transform infrared spectroscopy (FT-IR), digital microscope and scanning electron microscopy (SEM) techniques. The drug release kinetics was analyzed using Zero-order, First-order, Hixson-Crowell and Peppas models. The result indicated that the drug release rates highly depended on the polymers and pH medium. In addition, it was obtained that the combination of Carbopol 974P and gelatin retarded the drug release. So, these matrix tablets can reduce the dose intake. Thus, these matrix tablets are a promising release of donepezil HCl.



INTRODUCTION

Controlled drug delivery systems are attractive for researchers because of the difficulty and cost of developing new drugs. Developed drug delivery systems provide administering “active pharmaceutical ingredient (API) to the specific site of the body for drug delivery at the desired rate. Also, these systems are efficient in decreasing undesired side effects so they increase patient compliance. Among the different drug delivery

systems, oral controlled release (CR) formulation is the most preferred in the pharmaceutical industry.¹⁻³ Hydrogels are generally used in matrix tablets in light of their superior characteristics such as flexibility.⁴

Oral controlled release systems are one of the most desirable methods due to their low cost and risk of dose dumping and easy manufacturing route. Many polymers have been used in drug formulations as drug carriers. Carbomers (Carbopols®), anionic polymers with pH-dependent gelling properties, are being chosen in

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delivery systems.^{5,6} Three types of Carbopol[®] (974P, 971P and 71G), highly crosslinked and high molecular polymers, are widely used in the preparation of sustained release hydrophilic matrix tablets, and Carbopol[®] 974P is preferred primarily in systems where a sharp viscosity response is required.⁷⁻¹⁴ Carbopols are of increasing interest by researchers as matrix formers in the oral administration of sustained-release dosage forms and gastric retention systems.¹⁵⁻¹⁸ Stability and pH responsiveness are selective properties for controlled drug delivery systems.¹⁹⁻²¹ Sustained release tablets (SRT) are suitable for overcoming shortcomings because of bioavailability, shorter biological half-life and high solubility in water so SRT is known as the most effective dosage form for such Alzheimer's disease and controlled drug delivery systems are attractive for supporting human health care.^{22,23}

Alzheimer's disease (AD) is a progressive brain disease and is highly prevalent in society older aged.²⁴⁻²⁸ Donepezil is an acetylcholinesterase inhibitor most commonly used in the treatment of AD. Donepezil's high dose has significant side effects, gastrointestinal alterations, and hepatotoxicity.²⁹⁻³¹

Excipients such as gelatin, sodium alginate and cellulose are potentially useful in drug delivery systems. Gelatin is a biodegradable and eco-friendly polymer, so it has been chosen for controlled release systems. Zeolites have unique opened framework architecture so montmorillonite and some clays show a significant role in drug delivery systems.^{32,33} Sodium alginate because of nontoxic, biocompatible, biodegradable and swelling, mucoadhesive properties has been attractive for drug delivery.³⁴ Cellulose is hydroxyl-rich and has lots of three-dimensional hydrogen-bond networks which provide insoluble

properties in solvents and low reactivity and it is important in compression tablets as compressibility enhancer.^{35,36} Hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, is used as the main mineral component of health issues and biological fields such as bones or teeth.^{37,39}

The prime objective of the present work aims at developing Carbopol 974P based tablets for releasing systems using co-excipients like gelatin, α -cellulose, sodium alginate, hydroxyapatite and zeolite. The effects of excipient type and concentration on *in vitro* release of donepezil hydrochloride have also been investigated.

EXPERIMENTAL

Materials

Gelatin was purchased by Carlo Erba. Sodium alginate (Protonal LF 10/60) was purchased from FMC Biopolymer. Hydroxyapatite and α -cellulose (powder, 5 μm and surface area $\geq 100\text{m}^2/\text{g}$) were supplied from Sigma-Aldrich. Clinoptilolite was gifted by Gordes Zeolite Company. Carbopol 974P was obtained by Marmara Chemical Company. Sodium hydroxide and monobasic potassium phosphate were provided by J.T Baker. Sodium chloride and hydrochloric acid were supplied by Merck. Donepezil HCl was gifted by Abdi Ibrahim Company. All chemicals were used as received without further purification.

Preparation of Carbopol 974P based tablets

Sodium alginate, gelatin, α -cellulose, hydroxyapatite, natural zeolite (clinoptilolite), and carbopol were prepared in a clear and dry mortar. All the ingredients weighed accurately as per the formulation Table 1 and were mixed well. Drug and all the excipients were thoroughly blended in a mortar uniformly. Total ten formulations were made with ingredients. Donepezil hydrochloride loaded tablets were prepared by direct compression method. 0.5 g mixture fed manually into the pellet (tablet) pressing device. 120 kPa pressure was applied for

5 minutes to produce tablets. The prepared tablets were stored in the desiccator until further studies.

Table 1

Type of the Carbopol 974P based tablets

	Carbopol 974 P (w/w)	Sodium alginate (w/w)	Gelatin (w/w)	α -cellulose (w/w)	HAp (w/w)	Clinoptilolite (w/w)	Donepezil HCl (w/w)
Tablet 1 (T1)	99 %	-	-	-	-	-	1 %
Tablet 2 (T2)	80 %	19 %	-	-	-	-	1 %
Tablet 3 (T3)	80 %	-	19 %	-	-	-	1 %
Tablet 4 (T4)	80 %	-	-	19 %	-	-	1 %
Tablet 5 (T5)	80 %	-	-	-	19 %	-	1 %
Tablet 6 (T6)	80 %	-	-	-	-	19 %	1 %
Tablet 7 (T7)	80 %	9.5 %	9.5 %	-	-	-	1 %
Tablet 8 (T8)	80 %	-	9.5 %	9.5 %	-	-	1 %

Tablet 9 (T9)	80 %	-	9.5 %	-	9.5 %	-	1 %
Tablet 10 (T10)	80 %	-	9.5 %	-	-	9.5 %	1 %

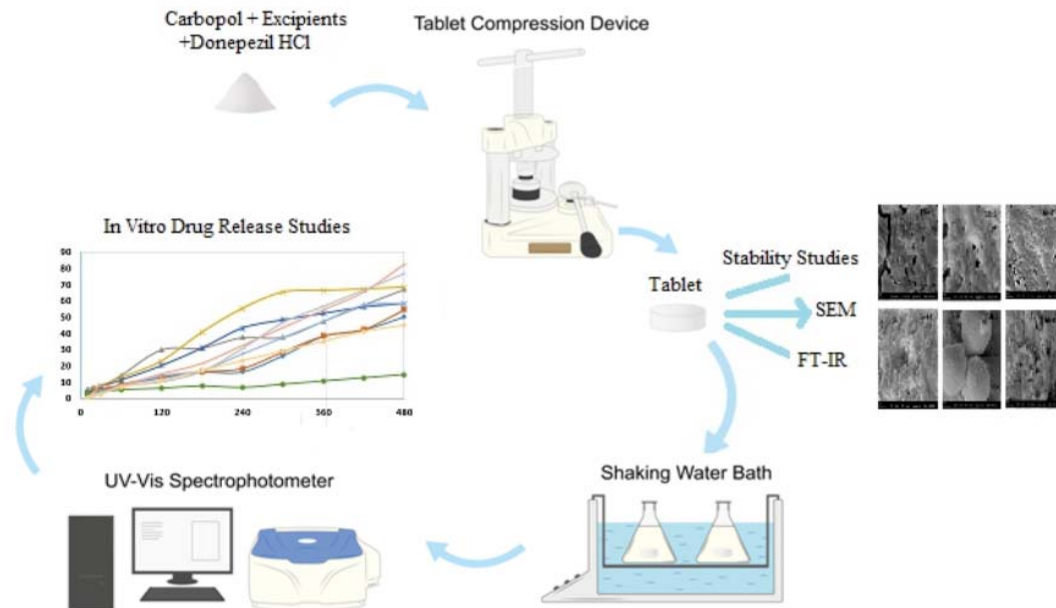


Fig. 1 – Experimental setup.

Characterization of the prepared tablets

The diameter and thickness of tablets were obtained by using digital microscope photos (Veho, VMS-004 USB Microscope). Characterization of chemical groups present in the tablets was performed by FT-IR spectroscopy (Perkin Elmer Spectrum 100). For each sample, a spectrum is obtained using the ATR utilizing a diamond internal reflection element mounted on a holder at a resolution of 4 cm^{-1} in the range $4,000\text{--}550\text{ cm}^{-1}$ for a total of 16 scans. SEM photographs were taken with JEOL JSM 6335F.

In vitro drug release

In vitro drug release tests were performed using pH 1.2, pH 6.8, and pH 7.4 buffer solutions at $37\pm 0.5^\circ\text{C}$. The basket was rotated at 50 rpm and 50 ml of dissolution medium was used. A single tablet was taken in 2 mL of dissolution media. The amount of donepezil hydrochloride released over time was determined by withdrawing samples at determined time intervals for 8 hrs. The withdrawn volume was substituted with a same amount of additional buffer. The measurements were performed in triplicate by using a UV-Vis spectrophotometer (Analytik Jena Specord 200/Plus) at 270 nm. The reproducibility of this approach is 1% to 3%. pH 1.2 buffer is prepared according to USP 29. Drug concentrations in the sample were determined from standard calibration curve. The complete experimental procedures of buffer solutions were reported previously.³

Kinetic evaluation

The data from the *in vitro* study were fitted to Zero order, First order, Hixson-Crowell and Peppas models to know the release profile. Zero order kinetics describes the process of constant drug release from a drug delivery system independent of the concentration. Where the release rate is concentration dependent, the first order equation is used to describe the

release from the system. The empirical equations are used to understand the dissolution mechanisms from the matrix.⁴⁰

Release of the drug is represented by the below equations:

$$\text{Zero order model: } Q_t = Q_0 + K_0 t \quad (1)$$

$$\text{First order model: } \log C_t = \log C_0 - k_1 t / 2.303 \quad (2)$$

$$\text{Hixson-Crowell model: } W_0^{1/3} - W_t^{1/3} = k_{\text{HC}} t \quad (3)$$

$$\text{Korsmeyer-Peppas model: } M/M_t = K_{\text{KP}} t^n \quad (4)$$

where Q_t is the amount of drug released at time t . Q_0 is the initial concentration of drug at time $t=0$. K_0 is the zero order release constant (Eq 1). In equation (2), C_0 is the initial concentration of the drug in the formulation and C_t is the concentration of drug in solution at time t and k_1 is first order rate constant expressed in units of time^{-1} . W_t is the mass of the drug molecule at time t , W_0 represents the initial weight of drug at time $t = 0$, and k_{HC} denotes the dissolution rate constant (Eq 3). In equation (4), M_t/M is fraction of drug released at time t , k_{KP} is the drug release rate constant, and n is the diffusional exponent.^{40,41}

Stability studies

Tablets were subjected to stability studies by storing them at $25^\circ\text{C} \pm 2^\circ\text{C}$ and $65 \pm 5\%$ Relative Humidity (RH) over a period of 3 months. At the end of study, the formulation was evaluated for drug content and *in vitro* release profile.

RESULTS AND DISCUSSION

Characterization of the prepared tablets

Digital microscope, FT-IR and scanning electron microscopy (SEM) were used to

characterize the tablets. Figures 2 and 3 show the images of FTIR spectrum of donepezil hydrochloride and tablets taken with the digital

microscope respectively. Thickness and diameter were 2.40 ± 0.05 and 0.20 ± 0.03 cm, respectively.

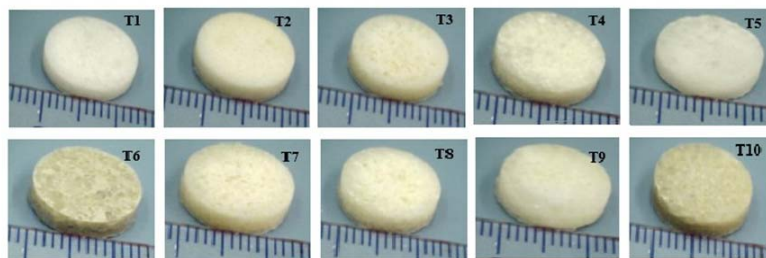


Fig. 2 – Digital microscope photos of tablets.

The functional groups of samples were studied using FTIR. The position of peak in FT-IR spectra of pure Donepezil Hydrochloride is compared with those in FT-IR spectra of Donepezil Hydrochloride plus excipients. It was observed that the characteristic peaks of Donepezil Hydrochloride were intact in the FTIR spectrum of Donepezil Hydrochloride with all the excipients used in the formulation. The C=O group in the donepezil hydrochloride forms an intensive absorption band around $1,680 \text{ cm}^{-1}$ and Carbopol has a characteristic band at $1,713 \text{ cm}^{-1}$ due to C=O stretching. In addition, Carbopol shows a characteristic band at $1,642 \text{ cm}^{-1}$ due to the carbonyl stretch of the carboxylic group of the polymers. So, the absorption band that ranges from $1,600 \text{ cm}^{-1}$ to $1,740 \text{ cm}^{-1}$ in all tablets is broad probably because of overlapping of C=O groups in the polymers and donepezil hydrochloride. The aliphatic C-H absorption is noticed from $2,900$ to $2,970 \text{ cm}^{-1}$. The observed band at around $1,450 \text{ cm}^{-1}$ was attributed to symmetric vibrations of carboxylate salt ions (T2, T5, T7 and T9). The band at 670 cm^{-1} is due to N-H bending (T3, T7, T8, T9 and T10).

Cellulose tends to be hydrophilic and thus strongly interacts with water, the broad absorption band seen between $3,000$ and $3,500 \text{ cm}^{-1}$ can be attributed is attributed to the OH groups. The strong peak around $1,037 \text{ cm}^{-1}$ is attributed to the stretching vibration of C–O–C in the α -cellulose (T4 and T8). HAp had intensive peaks between $1,460$ and $1,550 \text{ cm}^{-1}$ due to the CO_3^{2-} . The sharp absorption band between 860 and $1,260 \text{ cm}^{-1}$ confirmed the presence of Al-O bond in the structure (T6 and T10).

The morphology of samples was determined using SEM. SEM photographs of tablets are given in Fig. 4. Pure Carbopol tablet exhibits a large, open, channel-like structure. The presence of pores or irregular cavities was observed in the case of tablets 2 and 3 (presence of sodium alginate and gelatin). These pores allowed water to be absorbed, resulting in increased swelling ability. Furthermore, SEM images showed that integration of α -cellulose caused a less porous structure (Tablet 4). T5 presents a homogenous surface with spherical particles. SEM images demonstrated that the tablet surface became coarser and rougher with the addition of clinoptilolite (Tablet 6).

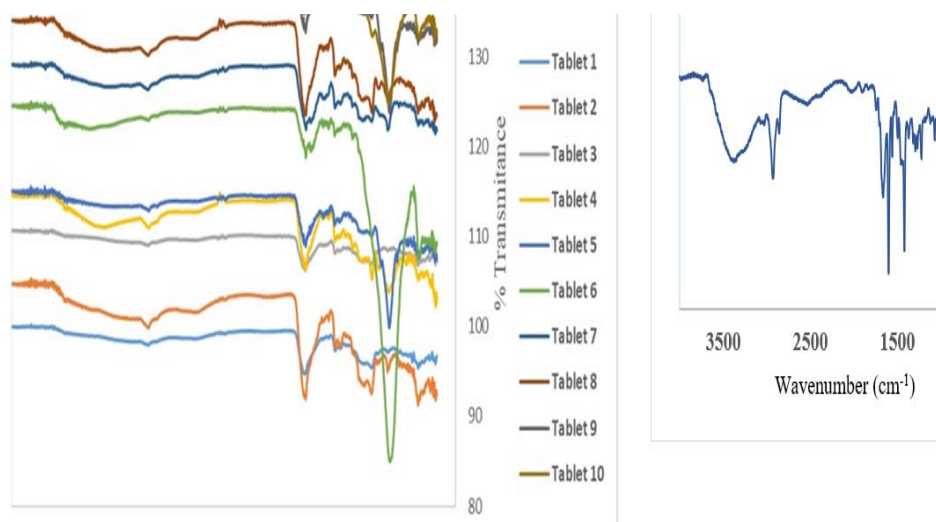


Fig. 3 – FT-IR analyses of Carbopol based tablets.

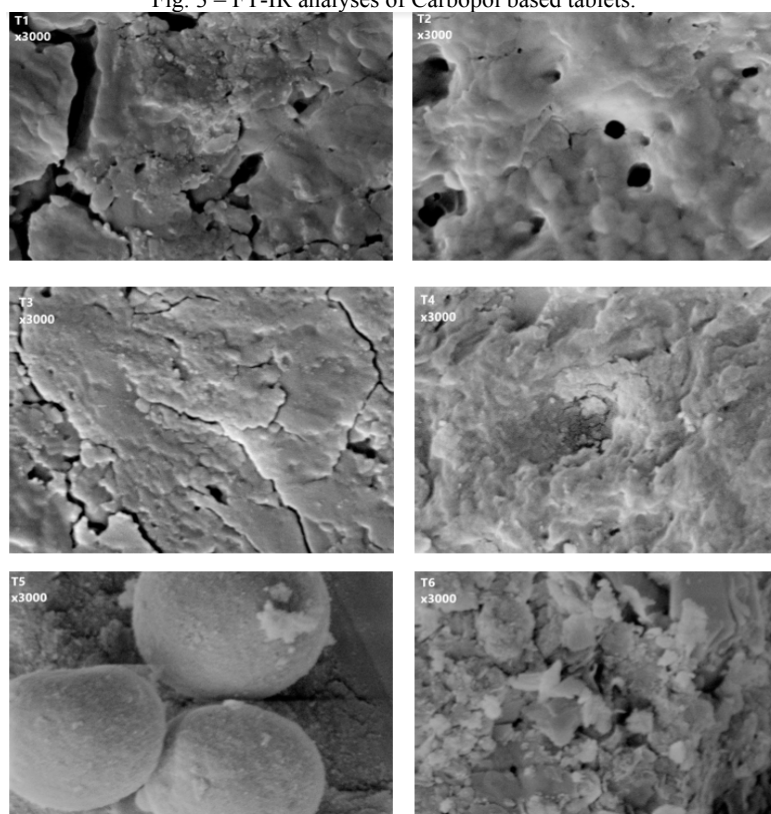


Fig. 4 – SEM images of tablets.

***In vitro* drug release studies**

In simulated gastric fluid (pH 1.2)

Figure 5 shows the percent cumulative release of donepezil HCl from tablets at pH 1.2. The addition of ingredients in tablet formulation, except clinoptilolite, resulted not only in an increase in the amount of drug released but also in a reduction of drug release rate. The combination of Carbopol 974P 5% and clinoptilolite 5% tablet (T6) did not retard the drug release and exhibited

the minimum percent cumulative release of donepezil HCl with 15% in 8 h. Gelatin exhibits a synergetic effect in release enhancement with α -cellulose. The *in vitro* drug release data for formulation T8 containing gelatin and α -cellulose with Carbopol 974P exhibited the maximum percent cumulative release of donepezil HCl with 82% for a prolonged duration (8 hr). This result is in line with previous studies showing that gelatin is a useful component in composites containing

materials ranging from ceramics to natural and synthetic polymers.⁴²

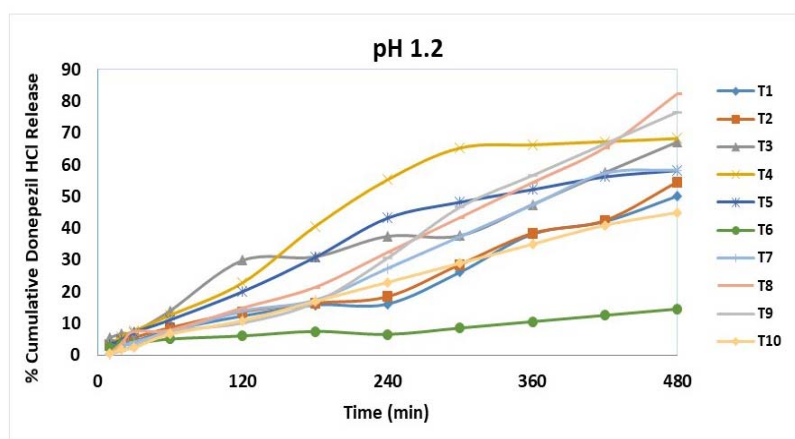


Fig. 5 – Donepezil HCl release profiles of matrix tablets at pH 1.2.

In simulated intestinal fluid (pH 6.8)

The percent cumulative release of donepezil HCl from tablets at pH 6.8 is shown in Fig. 6. Similarly, within a simulated gastric fluid, in-vitro release experiments in simulated intestinal fluid demonstrated that the release of donepezil HCl from all tablet formulations excluding clinoptilolite was generally sustained in the first 8 hours. The minimum release of the drug was obtained from T6

as was expected. Among all the formulations prepared, formulation T3 exhibit a maximum drug release of 87% at pH 6.8 in 8 h. In tablets containing gelatin, the drug was released from the polymer for a longer time and nearly maximum release was shown after 8 h. Changes in acid-base balance have a profound influence on many aspects of the action of drugs.

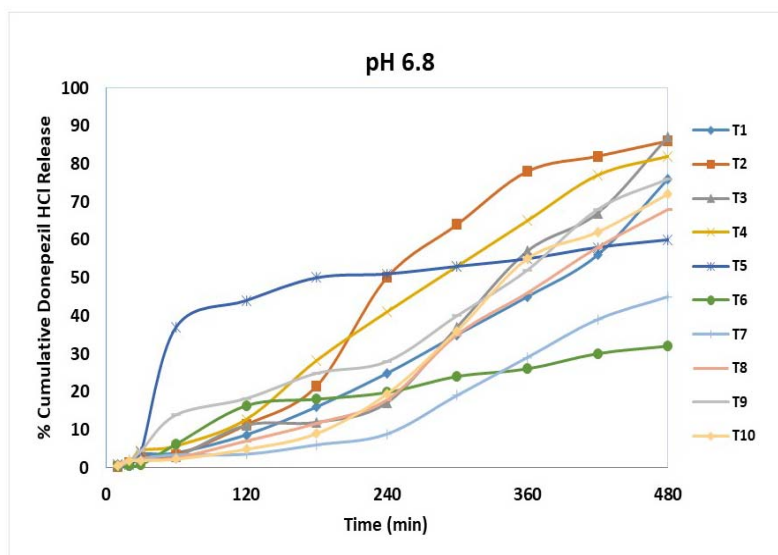


Fig. 6 – Donepezil HCl release profiles of matrix tablets at pH 6.8.

In simulated colon fluid (pH 7.4)

Donepezil HCl release from the matrix tablets was studied for 8 hours in simulated colon fluid. As can be seen in Fig. 7, the drug release profiles of formulations at pH 7.4 and pH 6.8 were found to

be closely similar. The results indicated that the presentation of gelatin in tablets caused higher drug retarding ability. T4 tablet showed 85% of donepezil HCl release at the end of 8 h. In tablets containing clinoptilolite, the drug was released

from the tablet in a shorter time and reached almost maximum release after 3h with 85%.

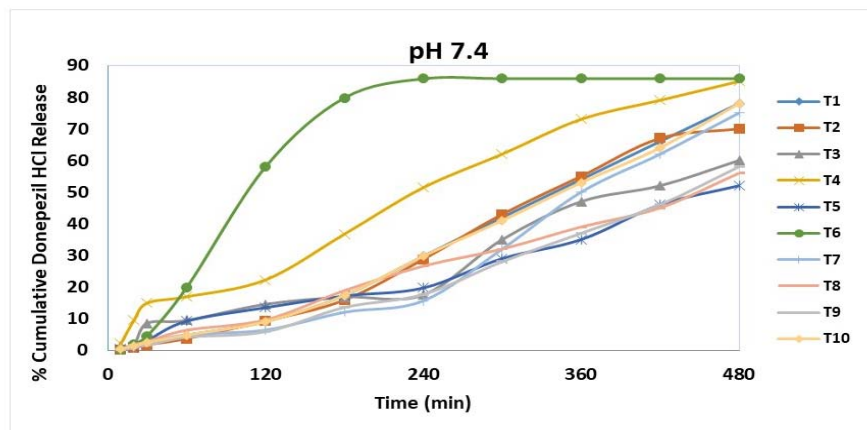


Fig. 7 – Donepezil HCl release profiles of matrix tablets at pH 7.4.

Donepezil HCl release kinetic tests

The release data was fitted into four models; Zero order, First-order, Hixson-Crowell and Korsmeyer-Peppas kinetic model to understand the release mechanism. The model that gives a higher R-squared value is considered the best fit for the release data. The kinetic values obtained for different formulations are indicated in Table 2. As

illustrated in Table 2, the best fit model changed according to ingredients and pH. But it is clear that the drug release data for all formulations fit well to the zero order kinetic (R^2 values ranged from 0.825 to 0.998) which indicates that the drug release is nearly independent of its concentration in the matrices.

Table 2

Kinetic models of tablets

	pH	Zero order		First order		Hixson-Crowell		Korsmeyer – Peppas			
		R^2	K_0 [mg/T]	R^2	K_1 [T ⁻¹]	R^2	K_s	R^2	n	k	Best Fit Model
T1	1.2	0.954	3.72×10^{-4}	0.737	2.070	0.820	0.0026	0.899	0.417	0.176	Zero order
	6.8	0.988	4.80×10^{-4}	0.408	1.953	0.984	0.0134	0.972	0.768	0.204	Zero order
	7.4	0.993	3.31×10^{-4}	0.398	1.809	0.946	0.0099	0.943	0.573	0.215	Zero order
T2	1.2	0.871	2.19×10^{-4}	0.682	1.979	0.951	0.0090	0.877	0.434	0.192	Hixson-Crowell
	6.8	0.998	4.71×10^{-4}	0.367	1.843	0.948	0.0129	0.914	0.746	0.223	Zero order
	7.4	0.987	5.15×10^{-4}	0.405	1.903	0.968	0.0139	0.966	0.798	0.217	Zero order
T3	1.2	0.942	4.35×10^{-4}	0.360	1.148	0.919	0.0090	0.938	0.423	0.382	Zero order
	6.8	0.948	4.72×10^{-4}	0.435	2.122	0.977	0.0136	0.960	0.810	0.180	Hixson-Crowell
	7.4	0.930	4.02×10^{-4}	0.523	1.757	0.966	0.0103	0.965	0.555	0.238	Hixson-Crowell
T4	1.2	0.893	4.50×10^{-4}	0.285	1.082	0.836	0.0095	0.859	0.450	0.403	Zero order
	6.8	0.966	4.32×10^{-4}	0.372	1.585	0.885	0.0113	0.891	0.627	0.275	Zero order
	7.4	0.923	3.97×10^{-4}	0.855	1.751	0.948	0.0113	0.914	0.391	0.399	Hixson-Crowell
T5	1.2	0.934	3.96×10^{-4}	0.849	2.062	0.887	0.0092	0.907	0.455	0.337	Zero order
	6.8	0.918	1.52×10^{-4}	0.939	0.955	0.932	0.0027	0.884	0.117	0.495	First order
	7.4	0.954	3.72×10^{-4}	0.986	2.602	0.985	0.0098	0.985	0.533	0.233	First order
T6	1.2	0.982	1.16×10^{-4}	0.953	2.550	0.820	0.0026	0.899	0.417	0.176	Zero order
	6.8	0.944	1.17×10^{-4}	0.787	2.493	0.853	0.006	0.846	0.375	0.183	Zero order

	7.4	0.825	2.97×10^{-4}	0.716	1.353	0.755	0.006	0.789	0.272	0.461	Zero order
T7	1.2	0.938	3.30×10^{-4}	0.966	2.684	0.939	0.0121	0.960	0.540	0.214	First order
	6.8	0.910	3.63×10^{-4}	0.976	4.036	0.971	0.0131	0.975	0.863	0.113	First order
	7.4	0.952	4.09×10^{-4}	0.478	2.163	0.992	0.0124	0.989	0.739	0.170	Hixson-Crowell
T8	1.2	0.929	4.74×10^{-4}	0.971	2.648	0.980	0.0114	0.967	0.609	0.258	Hixson-Crowell
	6.8	0.978	3.68×10^{-4}	0.421	2.282	0.985	0.0124	0.968	0.792	0.150	Hixson-Crowell
	7.4	0.986	4.37×10^{-4}	0.418	1.780	0.974	0.0118	0.978	0.651	0.231	Zero order
T9	1.2	0.951	5.44×10^{-4}	0.984	2.912	0.989	0.0132	0.990	0.696	0.243	Korsmeyer – Peppas
	6.8	0.993	2.18×10^{-4}	0.954	1.999	0.973	0.0059	0.970	0.325	0.267	Zero order
	7.4	0.961	4.47×10^{-4}	0.459	2.146	0.980	0.0133	0.983	0.802	0.177	Korsmeyer – Peppas
T10	1.2	0.928	3.39×10^{-4}	0.865	2.693	0.899	0.0100	0.925	0.560	0.212	Zero order
	6.8	0.934	2.75×10^{-4}	0.862	3.715	0.902	0.0112	0.942	0.795	0.128	Korsmeyer – Peppas
	7.4	0.974	3.38×10^{-4}	0.871	2.930	0.919	0.0105	0.925	0.621	0.202	Zero order

When the release data were analyzed according to Korsmeyer-Peppas equation, the n values for Carbopol 974P based tablet formulations ranged from 0.450 to 0.863 in simulated intestinal and colon fluid excluding T6. It can be inferred that the release mechanism was non-Fickian ($0.45 < n < 0.89$), indicating that the release was dependent on both drug diffusion and polymer relaxation. The release exponents were either less than 0.45 for all formulations from T1 to T6 in simulated gastric fluid. This situation showed that the drug release mechanism best fits the Fickian system because it exhibits a combination of the two mechanisms.

Stability studies

Stability studies showed that there was no significant change in appearance, drug content of formulations and the drug release profiles ($97.18 \pm 0.7\%$) at $25 \text{ }^\circ\text{C} \pm 2 \text{ }^\circ\text{C}$ over 3 months.

CONCLUSIONS

Matrix tablets based Carbopol 974P were successfully prepared by direct compression method. According to experimental results, as the environmental pH increased, more drug was released from the tablet. The results of *in vitro* drug release revealed that type of ingredients played an important role in the enhancement of drug release. Improvement in the drug release was seen by including co-excipients, excluding clinoptilolite. Clinoptilolite decreased the release rate of donepezil HCl. It was seen that the release of donepezil HCl was slower in formulation T8

containing α -cellulose and gelatin. Also, T3 at pH 6.8 exhibited the maximum percent cumulative release of donepezil HCl with 87% for prolonged duration (8 h). The present study demonstrates Carbopol 974P based tablets with added α -cellulose and gelatin can be successfully formulated for controlled delivery of donepezil HCl with desired release profile. However, it should not be forgotten that *in vivo* studies are needed to know whether the recommended formulation is going to be relevant.

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