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ORIGINAL ARTICLE

Oral Dissolving Film of Rivastigmine: Optimization Using Factorial Design

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Abstract

Purpose Due to impairments in memory and judgment, it is difficult for dementia patients to understand why they need medicine. Moreover, they often have swallowing difficulties. In this investigation, an oral dissolving film of rivastigmine tartrate (RT-ODF) was developed, offering a unique and convenient formulation for dementia patients.

Methods RT-ODF was developed using a solvent-casting technique. Sodium alginate and sodium carboxymethyl cellulose were used as film-forming polymers, and glycerol was used as a plasticizer. A full factorial design (3^2) was employed to estimate the impact of two factors at three levels: polymer concentration (1, 1.5, and 2% *w/v*) and plasticizer concentration (30, 40, and 50% *w/v*) on the responses, i.e., the tensile strength (TS), the disintegration time (DT), and the quantity of drug released (Q10 min).

Results The optimized formula (A1) that had the highest desirability value (0.923) exhibited the lowest tensile strength (3.67 ± 0.72 MPa), the shortest disintegration time (20 ± 2.0 s), and the highest percentage of drug released after 10 min (97.12 ± 2.01%). It was composed of 1% *w/v* sodium alginate (ALG-Na) and plasticized with 30% *w/v* glycerol. The pharmacokinetic study revealed that the RT-ODFs enhanced the drug's bioavailability by 1.91-fold relative to the reference product (Exelon® capsule).

Conclusion Oral dissolving films of rivastigmine tartrate could be a promising approach to promote drug bioavailability and convenience for geriatric patients.

Keywords Alzheimer's disease · Rivastigmine · Geriatric patients · Oral dissolving film · Patient compliance · 3^2 Factorial design

Introduction

Rivastigmine tartrate (RT) is indicated for the symptomatic treatment of mild-to-moderate Alzheimer's disease (AD) [1, 2]; this disease is characterized by fatal memory deterioration that is attributed to a significant deficiency of acetylcholine in the brain [3]. RT is an acetylcholinesterase inhibitor that promotes acetylcholine levels in the brain by suppressing both acetylcholinesterase and butyrylcholinesterase enzymes. RT is available as an oral solution, capsules, and transdermal patches [4]. The oral bioavailability of RT is mainly altered by first-pass metabolism. Besides, it is associated with the most frequent adverse effects such as nausea and abdominal pain [5].

Dementia patients may not be capable of taking their medications orally because of dysphagia, a major and often healthcare problem in geriatrics [6]. Moreover, most caregivers for dementia patients often encounter resistance to care in the early and middle stages of the disease because memory loss makes it difficult for patients to comprehend the need for medication. Helping a patient with dementia to take medication safely and easily can be challenging for him and his caregiver [7].

Fast-dissolving oral films (ODFs) represent an alternative for geriatric patients with dementia as a convenient way to administer when the film placed on the tongue would be

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immediately hydrated by saliva and in a few seconds disintegrate and dissolve to release the drug for trans-mucosal absorption. Fast-dissolving films offer a unique approach for dosing medications, especially for geriatric patients who suffer from swallowing difficulties, providing dose accuracy, avoiding the first-pass metabolism, and enhancing bioavailability, thus overcoming issues of poor patient compliance [8, 9].

ODFs are prepared with a film-forming polymer with the addition of a suitable plasticizer and other excipients aimed to optimize physicomechanical properties in terms of homogeneous texture, smooth surface and ductility, and disintegration time. The disintegration time of ODFs is valuable, as it has a significant impact on drug release and thereafter bioavailability [10].

The reported data from the literature indicate that the selection of polymer has a significant effect where an increase in polymer concentration results in disintegration time prolongation. Moreover, the plasticizer concentration affects the tensile strength of the film. In general, plasticizers are molecules that may interpose between the polymer chains allowing them to tilt and rotate freely, imparting higher flexibility. This is commonly observed in the form of films with high elongation and low tensile strength [11].

In this investigation, we have developed fast-dissolving oral films (ODFs) using a solvent-casting technique. Sodium alginate (ALG-Na) and sodium carboxymethyl cellulose (CMC) polymers were chosen depending on their good film-forming characteristics after preliminary studies were done (data was not shown). Glycerol was used as a proper plasticizer based on its ability to provide mechanical strength and flexibility to the film. Tween 80 is used as a surfactant having solubilizing and wetting properties, and sucralose was used as a sweetener.

The factorial design has played a valuable role in pharmaceutical formulations. It is valuable in investigating and understanding the impact of formulation variables on the characteristics of ODFs. A full factorial design (3^2) was implemented using Design-Expert® software v. 11. In this design, the concentration of polymer (F1) and plasticizer (F2) was chosen as independent variables, while the dependent variables were the tensile strength (TS) (R1), the disintegration time (DT) (R2), and the % RT released after 10 min (Q10 min).

Finally, the in vivo study was employed using albino male rabbits comparing the pharmacokinetics of RT from the optimized formula with that of the reference product (Exelon® capsule).

Materials and Methods

Materials

Rivastigmine tartrate (RT) was gifted from Eva Pharma (Cairo, Egypt). Sodium alginate (ALG-Na) was supplied by Sigma-Aldrich (UK). Sodium carboxymethylcellulose (CMC) was supplied by El Nasr Pharmaceutical Chemicals Company (ADWIC) (Qaliubiya, Egypt). Glycerol was purchased from Alpha Chemika (Mumbai, India). Tween 80 was obtained from MP Biomedicals (Santa Ana, CA, USA). Potassium dihydrogen phosphate was supplied by Dae-Jung Chemicals and Metals Company (Korea). Acetonitrile (HPLC grade) was supplied by Scharlau (Spain/European Union). Erythrosine (E127) (Eurocert Erythrosine 311807B20) was kindly donated by Minapharm Pharmaceuticals (Cairo, Egypt). Peppermint oil was donated by Medizen Pharmaceutical Industries (Alexandria, Egypt). Methanol (HPLC grade) was supplied from Fisher Scientific (UK). Glacial acetic acid, sodium hydroxide, and n-hexane were supplied from PioChem (Giza, Egypt). 1-Butanol was supplied from El Nasr Pharmaceutical Chemicals Company (ADWIC) (Qaliubiya, Egypt). DI water was collected from the Milli-Q-Millipore water system. All reagents were of analytical grade. The reference product was Exelon® capsule (3 mg) (EXP: 2022; LOT: BPF44) (Novartis Pharma AG, Basel, Switzerland).

Formulation Design of RT-ODFs

Differential Scanning Calorimetry (DSC)

DSC measurements of RT, polymers, glycerol, and the film matrix were performed using a DSC131 EVO (SETARAM Inc., France) in the heating zone of − 25 to 300 °C under a dry nitrogen gas purge and at a heating rate of 10 °C/min. The thermograms were built using CALISTO software v.149 [12].

Preparation of RT-Loaded ODFs (RT-ODFs)

RT-ODFs were developed by a solvent-casting technique [13]. In brief, a precisely weighed polymer was dissolved in DI water with continuous stirring until it became transparent. Subsequently, a solution of the desired amounts of the other ingredients was added to the resulting solution of polymer and was left aside for 24 h to remove any air bubbles. Then, the solution was cast into a petri dish (lubricate the petri dish with castor oil) and then dried into a film in the open air for 48 h. The films were cut into dimensions 2×2 cm^2, containing rivastigmine 3 mg (equivalent to 4.8 mg RT), and stored in aluminum foils.

Optimization of RT-ODFs

The two polymers that exhibited the shortest disintegration time and the lowest values of tensile strength were chosen to prepare RT-ODFs to be evaluated.

RT-ODFs were developed according to a full factorial design (3^2) to examine the impact of formulation variables

on the ODF characteristics applying Design-Expert® software v. 11.

In this design, two factors were evaluated, each at three levels; the experimental trials were performed at nine probable combinations. The independent variables investigated were the concentration of polymer (F1) and the concentration of plasticizer (F2), whereas the chosen dependent variables were the tensile strength (TS) (R1), the in vitro disintegration time (DT) (R2), and the % RT released after 10 min (Q10 min) (R3) as shown in Table 1.

Determination of Physicochemical Parameters of RT-ODFs

Weight

Three RT-ODFs of each formula were individually weighed on an electronic balance (AND HR 202, Tokyo, Japan) to estimate the average weight [9].

Film Thickness

The thickness of RT-ODF was measured by a micrometer screw gauge (Messwelk 0.01 mm, Germany). The thickness was tested at three different locations of each strip, and the average value was reported [12].

Surface pH

The pH was determined by moistening the RT-ODF with 1 mL of distilled water and kept for 1 min, then touching the pH electrode with its surface allowing equilibration for 1 min. Surface pH was measured using a pH meter (Jenway-3510, Staffordshire, UK) in triplicate [13].

Percentage Moisture Loss

The percentage moisture loss test was performed to ensure the physical stability and integrity of the film. The weight of six films of each formula was assessed accurately using an electronic balance (AND HR 202, Tokyo, Japan); then, they were kept in a desiccator for 3 consecutive days, and then, the weight was recorded again. Percentage moisture loss was estimated according to the following formula [14]:

$$\% \text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Uniformity of Drug Content

The drug content of each film was performed by dissolving the film in 100 mL of phosphate buffer pH = 6.8 with stirring using a magnetic stirrer for 1 h. This solution was filtered through a 0.45-µm membrane filter and then assayed using a validated HPLC method [4]. The results were presented as the mean of three values [10]. The assay was performed on an HPLC UltiMate 3000 system (Dionex Softron GmbH, Germany) equipped with a UV detector. Samples were injected onto a Kromasil 100 C18 (250 × 4.6 mm, 5 µm) column, delivered at a flow rate of 1 mL/min, and maintained at 25 °C. The mobile phase was composed of a mixture of 0.02 M potassium dihydrogen orthophosphate buffer (pH = 3.0) with o-phosphoric acid and acetonitrile at a ratio of 70:30 (*v*/*v*), and the injection volume was 20 µL. RT was quantified at 218 nm, and a standard calibration curve was plotted with a correlation coefficient (R^2) of 0.9995.

Disintegration Test

In vitro disintegration time of the RT-ODFs was determined in a beaker of 25 mL distilled water at 37 ± 0.5 °C swirling every 10 s. The disintegration time is defined as the time required for the film to disintegrate into small pieces. The test was repeated three times [10].

Mechanical Properties

The mechanical characteristics of the developed films including tensile strength (TS) and percent elongation at (% E) break were determined using Zwick 1425 material testing machine (Germany). The measurements were done in triplicate for each formula [10].

Table 1 Full factorial design for optimization of RT-ODFs

Factors (independent variables)	Levels		
F1: concentration of polymer	Low (1%)	Medium (1.5%)	High (2%)
F2: concentration of plasticizer	Low (30%)	Medium (40%)	High (50%)
Responses (dependent variables)	**Desirability constraints**		
R1: TS (MPa)	Minimize		
R2: DT (s)	Minimize		
R3: Q10 min (%)	Maximize		

In Vitro Dissolution Profile of RT-ODFs

The dissolution test of the RT-ODFs was performed using a USP Dissolution Apparatus I (Basket Apparatus) (Hanson SR8 plus, Chatsworth, CA, USA) at a rotation speed of 100 rpm in 900 mL of phosphate buffer pH = 6.8 maintained at 37 ± 0.5 °C [15, 16]. Samples of RT-ODFs, equivalently containing 4.8 mg (2 × 2 cm^2) of RT, were placed in baskets. Three milliliters of samples was withdrawn and replaced with a fresh medium. RT was assayed using HPLC as described before. All experiments were performed in triplicate. The % drug released was calculated using the standard calibration curve of RT in phosphate buffer pH = 6.8. The linearity of the standard calibration curve was appropriately in the range of 0.5–5 µg/mL ($Y = 0.3247\ X$, $R^2 = 0.9995$). The graphs were plotted to compare the % drug released versus time.

Statistical Analysis

All determinations were done in triplicate, and the values were expressed as mean ± SD. Data analysis was done by applying one-way analysis of variance (ANOVA) followed by Tukey test. A value of $p < 0.05$ was considered significant. The "Graph Pad InStat Demo v." software was used for this purpose.

Scanning Electron Microscopy (SEM)

The surface morphology of the optimized RT-ODF was examined using a JEOL JSM-5200 scanning electron microscope (Tokyo, Japan) operating at 25 kV. The samples were coated under vacuum with gold under an argon atmosphere before the examination. The micrographs were observed to study the morphological and surface characteristics of RT and the RT-ODF [12].

Stability Studies

According to ICH guidelines, stability studies were conducted at 40 ± 2 °C with relative humidity RH 75 ± 5% to investigate the impact of temperature and relative humidity on the drug in the optimized formula. The films were enveloped in an aluminum wrap in a glass container. The container was stored for 90 days. After the storage time, the films were evaluated concerning their appearance, disintegration time in addition to their drug content, and in vitro drug release.

Statistical analysis of data was employed using paired sample *t*-test. Any variation was considered significant at $p < 0.05$. The "Graph Pad InStat Demo v." software was adopted for analysis [17, 18].

Determination of Pharmacokinetic Parameters in Rabbits

Pharmacokinetic Study

The study was conducted to determine the pharmacokinetics of RT after oral administration of the optimized ODF formula compared to that of the reference product Exelon® 3 mg capsule. The experimental procedure and the in vivo study protocol were reviewed and approved by the Research Ethics Committee (REC) at the Faculty of Pharmacy, Cairo University, Egypt, on 29 October 2018 (REC Approval No. is PI (2286)). Twelve adult New Zealand male white rabbits, weighing 3.0 ± 0.5 kg, were housed individually and had free access to food and water.

A single dose of the drug was given to New Zealand male rabbits using a two-way crossover design with a washout period of 7 days between the two doses. During the first phase, rabbits received either the reference product (Exelon® capsule) or the optimized formula. In the second phase, rabbits, that administered the optimized formula first, received the reference product or vice versa [19]. Twelve rabbits were randomly divided into two groups each containing six rabbits. The first group received the reference product Exelon® capsule. Five milliliters of water was given to the rabbits to facilitate swallowing the dose. The second group received the selected RT-ODF formula, which was placed above the rabbit's tongue and allowed to dissolve in saliva. Blood samples (2 mL) were obtained from the retro-orbital plexus of rabbits [20, 21].

Before dose administration, rabbits fasted overnight for 10 h. Following drug administration, serial aliquots of blood samples were withdrawn at periodic time intervals of 0, 0.08, 0.17, 0.25, 0.5, 1, 2, 4, and 6 h.

Blood samples were collected in heparinized tubes, and plasma was immediately harvested by centrifugation at 3000 rpm for 15 min at room temperature using a centrifuge (Universal 16, Hettich, Germany). Separated plasma was directly aspirated and transferred into plastic tubes and was stored at − 20 °C till analyzed.

Extraction Procedure

Extraction was performed by adding 100 µL of 1 M NaOH and 3 mL of 1-butanol/*n*-hexane (2: 98, *v*/*v*) to 1 mL of plasma. After centrifugation at 6000 rpm, the whole organic layer was separated. Then, 600 µL of 0.1% acetic acid was added. The mixture was vortex-mixed and centrifuged. The aqueous phase was analyzed for RT [22].

High-Performance Liquid Chromatography (HPLC) Analysis of RT in Plasma

Plasma samples were analyzed for RT using a validated HPLC method. An Agilent 1260 Infinity II HPLC apparatus (Santa Clara, CA, USA) consisted of Quat-pump, 1260 Vial-sampler, and a fluorescence detector (1260 FLD Spectra). Data were collected and analyzed by OpenLAB software (v. A.01.05; Agilent Technologies). Samples of RT in plasma were injected onto a Sep-Tech ST150-10-C18 (250 × 4.6 mm) column and delivered at a flow rate of 1 mL/min at room temperature (25 °C). The mobile phase was a mixture of 0.02 M potassium dihydrogen orthophosphate buffer (pH = 3.0) with o-phosphoric acid and acetonitrile at a ratio of 70: 30 (*v*/*v*), the injection volume was 100 µL, and the detection of RT was carried out at an excitation wavelength (λ_{exc}) of 220 nm and emission wavelength (λ_{em}) of 293 nm [23]. The % drug released was calculated using a standard calibration curve of RT in plasma. The linearity of the standard calibration curve was found in the range of 15–480 ng/mL ($Y = 0.0359\ X$, $R^2 = 0.998$]. The graphs were plotted to compare the % drug released versus time.

Pharmacokinetic Analysis

Non-compartmental pharmacokinetic analysis was carried out using WinNonlin® 5.2 (Pharsight Corporation) [24]. The maximum plasma concentration (C_{max}, ng/mL), the time taken to reach maximum plasma concentration (T_{max}, h), the area under the plasma concentration–time curve ($AUC_{0-\infty}$, ng h/mL), the $t_{1/2}$ (h) which was calculated as 0.693/Ke, the mean residence time (MRT, h), and the elimination rate constant (Ke, h^{-1}) after oral administration were determined. The data were expressed as the mean ± standard deviation. Data were analyzed using one-way ANOVA adopting the "Graph Pad InStat Demo v." software. The significance of the difference will be determined at the 95% confidence limit ($\alpha = 0.05$).

Results and Discussion

In the pre-formulation studies, attention was given to the selection of a proper polymer at a suitable concentration to prepare a blank film that had good ductility and flexibility and could disintegrate fast [12]. The preliminary screening of familiar polymers in the literature revealed that ALG-Na, carrageenan, polyvinyl alcohol (PVA), and CMC had good film-forming capacity at certain concentrations. Obtained films were homogenous, smooth, non-sticky, and transparent. The disintegration time and tensile strength of the film are the most important characteristics for evaluating the ODFs [12]. It was clear that films made by ALG-Na and CMC had lower tensile stress values and disintegrated more rapidly than those prepared by carrageenan and polyvinyl alcohol (PVA). Data was not shown here.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of RT, polymers, glycerol, and the film matrix are shown in Fig. 1. DSC test was used to evaluate drug compatibility with formula components. When the endothermic peak of the drug was shifted, it might indicate the interaction of drug molecules with other excipients [25]. DSC showed no interaction between RT and ALG-Na in the optimized formulae (A1).

Preparation of RT-ODFs

The solvent-casting technique is the most frequent approach for the manufacturing of ODFs due to the ease of the technique and its low cost [26]. In this casting study, we selected hydrophilic polymers that produce homogenous and flexible films, easily removable from the casting support. Glycerol was selected as a plasticizer as it developed transparent homogenous and flexible preparation with good mechanical strength. The compositions of RT-ODFs are depicted in Table 2.

Factorial Design Analysis

In an attempt to improve the developed formulae, factorial design is a valuable tool to reduce the number of experiments and investigate the relationship between investigated factors and responses of interest [26]. It was found that the polymer and plasticizer concentrations were the most effective factors in the previous literature that affected the disintegration time and drug release. Depending on the results of preliminary trials, ALG-Na and CMC were chosen to be included in the factorial design. Nine experimental runs were assigned, A1–A9 and C1–C9 for ALG-Na and CMC polymers, respectively. The responses of the experimental runs are shown in Tables 3 and 4.

Effect of Formulation Variables on Tensile Strength (TS)

Tensile strength is defined as the maximum tension force that a material can withstand during stretching before tearing up. Hence, it is important to optimize the polymeric blends to afford enough tensile strength to endure the stress along with the production, packaging, transport, and handling process [25, 26].

From Tables 3 and 4, it was found that the tensile strength of formulae A1–A9 ranged from 3.67 ± 0.72 to 5.83 ± 0.68 MPa, whereas the tensile strength of formulae

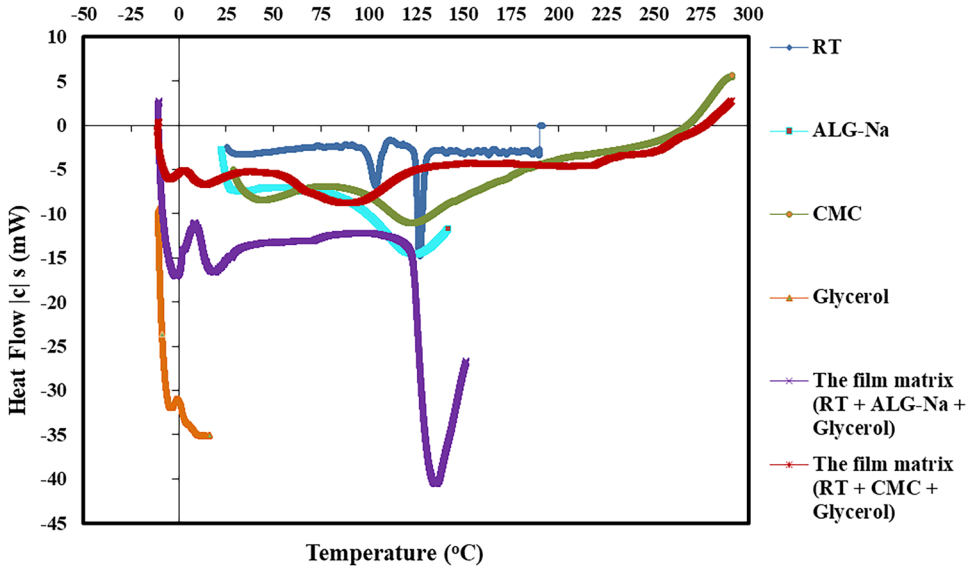

Fig. 1 DSC thermograms of RT, polymers, glycerol, and the film matrix

C1–C9 was in the range of 7.07 ± 0.46 to 11.37 ± 0.25 MPa. The influence of the independent variables on the tensile strength of RT-ODFs is demonstrated in Fig. 2.

It was revealed that the concentration of polymer and plasticizer significantly affected the tensile strength of the prepared formulae ($p = 0.0002$).

Regarding the polymer concentration, it was found that reducing the concentration of the polymer decreased the TS value of the film which was in an agreement with Alhayali et al. (2019). The lowest tensile strength was obtained as the polymer concentration was 1% *w/v*.

On the other hand, plasticizer content showed no significant effect on the TS values of ALG-Na formulae.

However, in the case of CMC formulae, TS was affected by plasticizer concentration. It was found that increasing the plasticizer content decreased the TS value because small

Table 2 Composition of RT-ODFs

Formula code		**Ingredients**							
	RT (mg/film)	ALG-Na (mg)	CMC (mg)	Glycerol (mg)	Tween 80 (mg)	Sucralose (mg)	Peppermint oil (mg)	Coloring agent (mg)	Water (mL)
A1	4.8	100	-	30	10	100	80	10	10
A2	4.8	150	-	45	10	100	80	10	10
A3	4.8	200	-	60	10	100	80	10	10
A4	4.8	100	-	40	10	100	80	10	10
A5	4.8	150	-	60	10	100	80	10	10
A6	4.8	200	-	80	10	100	80	10	10
A7	4.8	100	-	50	10	100	80	10	10
A8	4.8	150	-	75	10	100	80	10	10
A9	4.8	200	-	100	10	100	80	10	10
C1	4.8	-	100	30	10	100	80	10	10
C2	4.8	-	150	45	10	100	80	10	10
C3	4.8	-	200	60	10	100	80	10	10
C4	4.8	-	100	40	10	100	80	10	10
C5	4.8	-	150	60	10	100	80	10	10
C6	4.8	-	200	80	10	100	80	10	10
C7	4.8	-	100	50	10	100	80	10	10
C8	4.8	-	150	75	10	100	80	10	10
C9	4.8	-	200	100	10	100	80	10	10

Table 3 Experimental runs, independent variables, and measured responses of the full factorial experimental design of RT-ODFs using ALG-Na polymer. Data represent the mean value ± SD ($n = 3$)

Formula code	F1: polymer concentration	F2: plasticizer concentration	R1: tensile strength (MPa)	R2: disintegration time (s)	R3: Q10 min (%)
A1	Low	Low	3.67 ± 0.72	20 ± 2.0	97.12 ± 2.01
A2	Medium	Low	5.59 ± 0.45	24 ± 0.6	79.98 ± 4.95
A3	High	Low	5.35 ± 0.31	93 ± 2.9	78.84 ± 0.87
A4	Low	Medium	4.57 ± 0.38	24 ± 0.6	95.41 ± 3.45
A5	Medium	Medium	5.02 ± 0.24	31 ± 1.7	72.74 ± 2.43
A6	High	Medium	5.83 ± 0.68	91 ± 1.2	68.56 ± 1.51
A7	Low	High	4.85 ± 0.71	25 ± 0.6	91.41 ± 3.47
A8	Medium	High	5.63 ± 0.12	46 ± 1.2	70.65 ± 3.45
A9	High	High	5.67 ± 0.08	99 ± 1.2	66.46 ± 4.01

molecules of plasticizer could simply incorporate into polymer molecular chains, resulting in more free space and thus enhancing the mobility of the polymer chains. This in turn reduces the glass transition temperature (T_g) and eventually improves the elasticity of the film [27, 28].

Effect of Formulation Variables on In Vitro Disintegration Time (DT)

Disintegration is considered one of the most critical quality aspects to guarantee patient compliance and acceptance of the ODFs [12]. Tables 3 and 4 show that the DT of formulae prepared with ALG-Na polymer ranged from 20 ± 2.0 to 99 ± 1.2 s, whereas the DT of formulae prepared with CMC was in the range of 24.33 ± 1.16 to 147.70 ± 2.52 s. The disintegration time of some formulae exceeded the recommended FDA limit (30 s) [29]. The effect of the independent variables on the DT of RT-ODFs is shown in Fig. 3.

It was clear that the polymer and plasticizer concentration had significant impacts on the DT of the prepared formulae ($p < 0.0001$).

The results suggested that increasing the polymer concentration resulted in increasing the DT of the prepared formulae. This could be attributed to high polymer concentration which constituted a viscous gel that retard the penetration of the disintegration medium thereby prolonging the disintegration time [28, 30].

It was obvious that the disintegration time was dependent on the plasticizer concentration. This means that an increase in the plasticizer content resulted in increasing the disintegration time.

Effect of Formulation Variables on the Amount of Drug Released After 10 min (Q10 min)

The percentage of the drug released from formulae prepared with ALG-Na polymer after 10 min (Q10 min) ranged from 66.46 ± 4.01 to 97.12 ± 2.01% as shown in Table 3. Whereas for formulae prepared with CMC, the Q10 min ranged from 49.48 ± 4.15 to 85.09 ± 4.93% as depicted in Table 4. The effect of the two independent variables on the Q10 min of RT-ODFs is demonstrated in Fig. 4.

The results revealed that both the polymer and plasticizer concentrations exhibited significant impacts on the Q10 min of the developed formulae ($p < 0.0001$).

The amount of drug released was directly affected by the polymer concentration. It was found that the release of the drug increased at the lowest polymer concentration

Table 4 Experimental runs, independent variables, and measured responses of the full factorial experimental design of RT-ODFs using CMC polymer. Data represent the mean value ± SD ($n = 3$)

Formula code	F1: polymer concentration	F2: plasticizer concentration	R1: tensile strength (MPa)	R2: disintegration time (s)	R3: Q10 min (%)
C1	Low	Low	9.50 ± 0.70	24.33 ± 1.16	85.09 ± 4.93
C2	Medium	Low	11.00 ± 1.31	30.33 ± 1.53	64.31 ± 2.49
C3	High	Low	7.93 ± 0.38	91.67 ± 2.08	61.07 ± 0.88
C4	Low	Medium	8.20 ± 0.85	40.33 ± 1.53	71.51 ± 2.35
C5	Medium	Medium	10.47 ± 0.81	91.00 ± 1.73	50.57 ± 2.19
C6	High	Medium	11.37 ± 0.25	100.30 ± 1.53	51.95 ± 2.27
C7	Low	High	7.07 ± 0.46	42.33 ± 2.08	75.11 ± 2.34
C8	Medium	High	8.70 ± 0.20	101.70 ± 2.89	52.08 ± 2.17
C9	High	High	8.93 ± 0.06	147.70 ± 2.52	49.48 ± 4.15

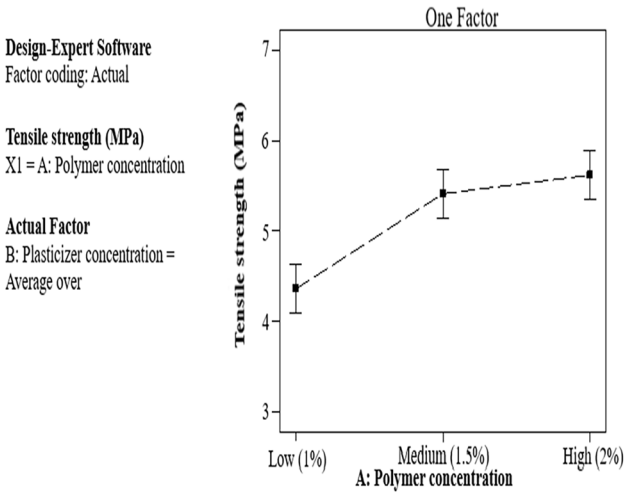

Fig. 2 Effect of polymer concentration on the tensile strength of RT-ODFs using ALG-Na polymer

(1% *w/v*) due to the increased dissolution at low polymer concentration leading to a minimum quantity of fluid desired to dissolve the polymer in addition to the hydrophilic polymer created pores for the drug to diffuse out of the film thus promoting the release of the drug [9].

On the other hand, the dissolution of the drug decreased at higher polymer concentrations. This might be due to the creation of a gel-like barrier surrounding the drug and hence, retaining it inside the polymer matrix leading to a slower drug release as reported in the literature for fast-dissolving oral films [9, 30–32].

The amount of drug released decreased with increased plasticizer concentration which was in agreement with the data mentioned by Maher et al. [32].

Optimization of RT-ODFs

Generally, the purpose of optimization of any pharmaceutical formula is to specify the levels of variables needed to get a good quality product. RT-ODFs were optimized for the responses R_1 (TS), R_2 (DT), and R_3 (Q10 min). The target was to minimize TS and DT in addition to maximizing the Q10 min. The optimal values of the variables were

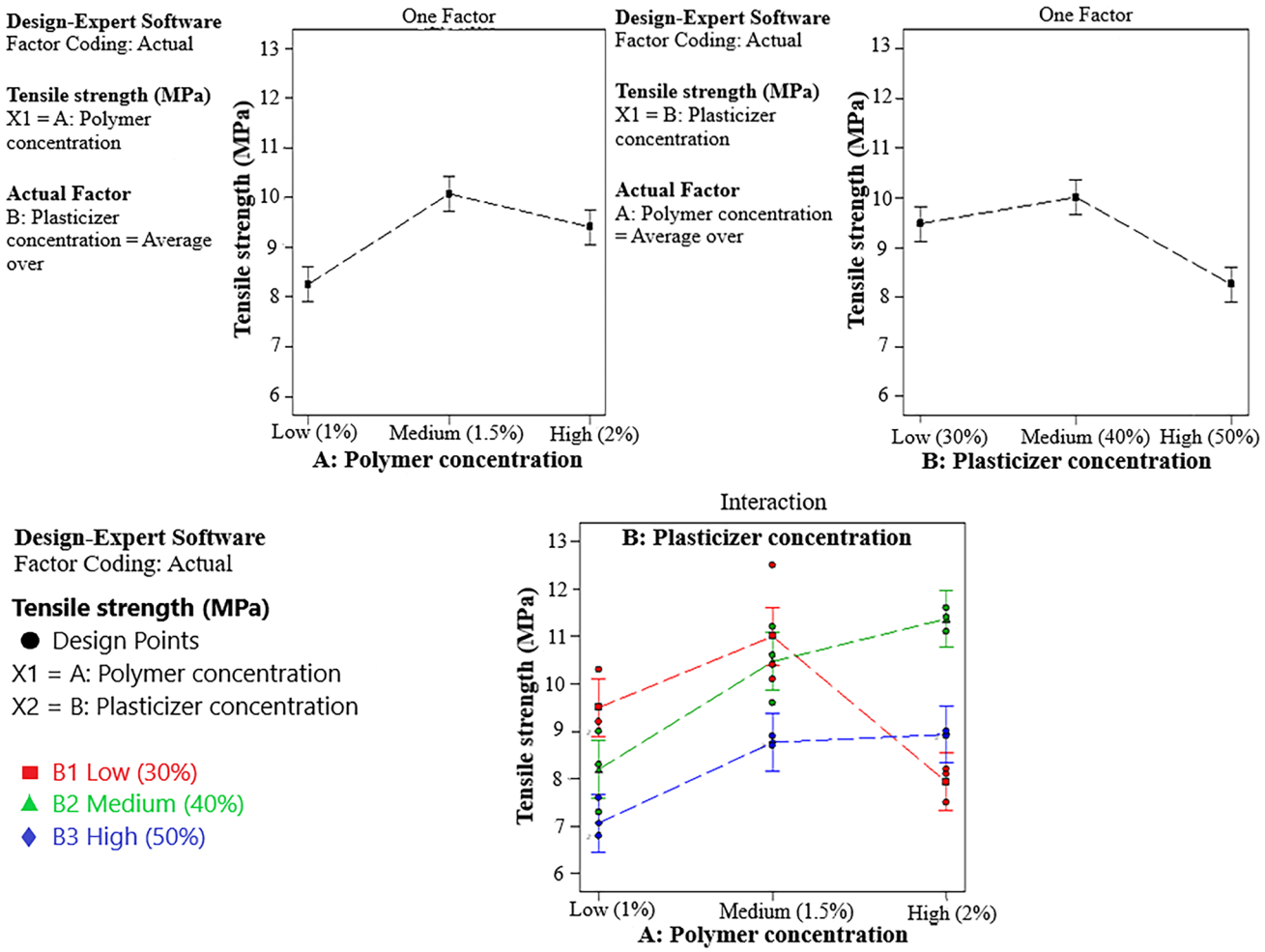

Fig. 3 Effect of formulation variables on the tensile strength of RT-ODFs using CMC polymer

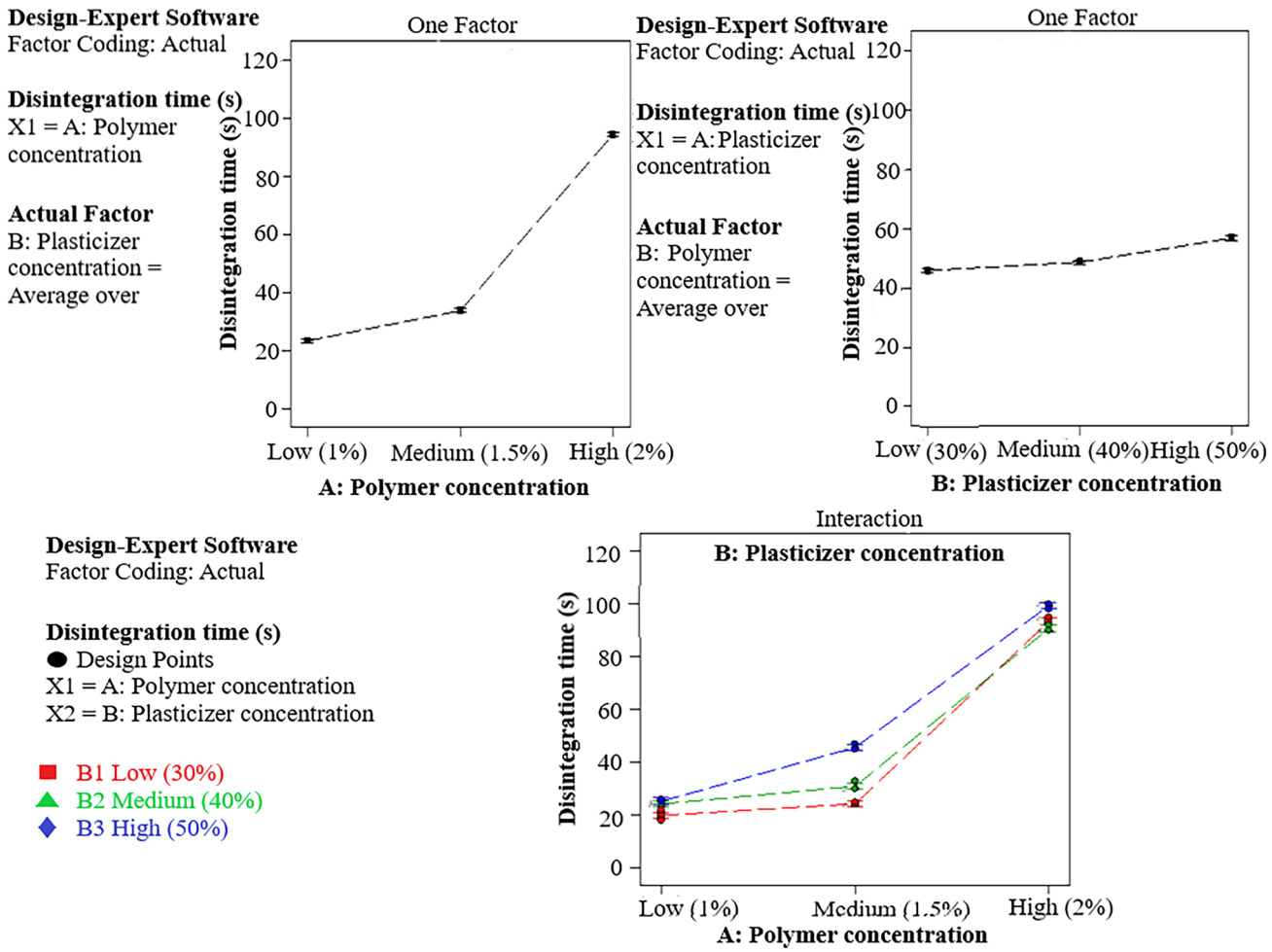

Fig. 4 Effect of formulation variables on the disintegration time of RT-ODFs using ALG-Na polymer

developed by numerical optimization using the Design-Expert® software v. 11 depending on the desirability criterion. It was obvious that the formulae A1 and C1 had the highest desirability values, 0.923 and 0.847, respectively, as shown in Tables 5 and 6. Hence, A1 was selected for further in vivo study as it exhibited the lowest tensile strength (3.67 ± 0.72 MPa), the shortest disintegration time (20 ± 2.0 s), and the highest percentage of drug released after 10 min (97.12 ± 2.01%). The optimized formula (A1) was composed of 1% *w/v* ALG-Na polymer and plasticized with 30% *w/v* glycerol.

Table 5 Optimization of RT-ODFs using ALG-Na polymer

Number	Polymer concentration	Plasticizer concentration	Tensile strength	Disintegration time	Q10 min	Desirability	
1	Low (1%)	Low (30%)	4.361	20.000	99.304	0.923	Selected
2	Low (1%)	Medium (40%)	4.361	24.333	93.714	0.847	
3	Low (1%)	High (50%)	4.361	25.333	90.922	0.810	
4	Medium (1.5%)	Low (30%)	5.412	24.333	78.353	0.576	
5	Medium (1.5%)	Medium (40%)	5.412	31.000	72.763	0.464	
6	Medium (1.5%)	High (50%)	5.412	45.667	69.971	0.369	
7	High (2%)	Low (30%)	5.618	93.333	76.006	0.190	
8	High (2%)	Medium (40%)	5.618	90.667	70.416	0.176	
9	High (2%)	High (50%)	5.618	99.333	67.624	0.049	

Table 6 Optimization of RT-ODFs using CMC polymer

Number	Polymer concentration	Plasticizer concentration	Tensile strength	Disintegration time	Q10 min	Desirability	
1	Low (1%)	Low (30%)	9.500	24.333	85.043	0.847	Selected
2	Low (1%)	High (50%)	7.067	42.333	73.777	0.765	
3	Low (1%)	Medium (40%)	8.200	40.333	72.897	0.732	
4	Medium (1.5%)	Low (30%)	11.000	30.333	63.458	0.537	
5	High (2%)	Low (30%)	7.933	91.667	61.973	0.463	
6	Medium (1.5%)	High (50%)	8.767	101.667	52.193	0.292	
7	Medium (1.5%)	Medium (40%)	10.467	91.000	51.313	0.273	
8	High (2%)	Medium (40%)	11.367	100.333	49.827	0.207	
9	High (2%)	High (50%)	8.933	147.667	50.707	0.075	

Determination of Physicochemical Parameters of RT-ODFs

RT-ODFs were evaluated according to the following parameters: weight variation, thickness, surface pH, moisture loss, and drug content.

Weight

The weight of formulae of A1–A9 was found in the range of 74.10 ± 0.56 to 121.87 ± 4.08 mg while the formulae C1–C9 ranged from 76.20 ± 0.62 to 122.17 ± 1.75 mg as shown in Tables 7 and 8, indicating the uniformity in the distribution of drug as well as excipients.

Film Thickness

Thickness values of the formulae A1–A9 were found to be 0.11 ± 0.01 to 0.25 ± 0.01 mm while the formulae C1–C9 ranged from 0.12 ± 0.01 to 0.21 ± 0.01 mm as shown in Tables 7 and 8, indicating uniform cast of respective formulae. It was observed that there is a significant increase in the film thickness ($p < 0.0001$) as the polymer concentration increased.

Surface pH

The surface pH of ODFs is one of the indicators of patient compliance. It should be close to saliva pH to avoid any irritability to the oral mucosa. The surface pH of the formulae A1–A9 was found to be in the range of 5.47 ± 0.01 to 5.86 ± 0.03 while the formulae C1–C9 ranged from 5.81 ± 0.02 to 6.74 ± 0.01 which was within acceptable limits as depicted in Tables 7 and 8.

Percentage Moisture Loss

The formulae A1–A9 showed a moisture loss in the range of 1.15 ± 0.46 to 2.30 ± 0.33% while C1–C9 showed a moisture loss ranging from 0.98 ± 0.15 to 2.15 ± 0.29% as shown in Tables 7 and 8, which indicates good physical stability and integrity of the films.

Table 7 Data of evaluation parameters of RT-ODFs prepared with ALG-Na. Data represent the mean value ± SD ($n = 3$) and moisture loss data ($n = 6$)

Formula code	Thickness (mm)	Elongation (%)	Weight variation (mg)	Drug content (%)	Surface pH	Moisture loss (%)
A1	0.11 ± 0.01	68.67 ± 26.1	74.10 ± 0.56	104.52 ± 1.23	5.55 ± 0.03	1.80 ± 0.22
A2	0.13 ± 0.01	65.67 ± 24.54	97.87 ± 0.59	96.42 ± 1.28	5.47 ± 0.01	1.35 ± 0.25
A3	0.22 ± 0.02	60.33 ± 17.39	113.87 ± 0.40	102.89 ± 0.40	5.86 ± 0.03	1.32 ± 0.15
A4	0.12 ± 0.01	69.33 ± 11.93	87.67 ± 1.05	95.35 ± 1.37	5.61 ± 0.02	2.30 ± 0.33
A5	0.14 ± 0.00	63.00 ± 17.06	99.43 ± 0.32	102.90 ± 2.19	5.47 ± 0.01	1.15 ± 0.46
A6	0.22 ± 0.01	68.33 ± 26.58	120.97 ± 1.07	101.23 ± 1.97	5.77 ± 0.02	1.51 ± 0.25
A7	0.15 ± 0.01	57.50 ± 9.19	91.07 ± 0.84	97.97 ± 2.21	5.47 ± 0.02	1.16 ± 0.28
A8	0.20 ± 0.01	70.00 ± 12.17	109.53 ± 0.40	95.54 ± 1.65	5.67 ± 0.02	1.66 ± 0.16
A9	0.25 ± 0.01	60.67 ± 14.01	121.87 ± 4.08	108.12 ± 1.22	5.73 ± 0.04	1.35 ± 0.19

Table 8 Data of evaluation parameters of RT-ODFs prepared with CMC. Data represent the mean value ± SD ($n = 3$) and moisture loss data ($n = 6$)

Formula code	Thickness (mm)	Elongation (%)	Weight variation (mg)	Drug content (%)	Surface pH	Moisture loss (%)
C1	0.12 ± 0.01	135.33 ± 25.58	81.17 ± 7.22	104.37 ± 2.00	5.81 ± 0.02	1.37 ± 0.28
C2	0.14 ± 0.01	84.33 ± 21.73	98.77 ± 0.25	99.13 ± 2.48	5.83 ± 0.03	1.41 ± 0.20
C3	0.18 ± 0.01	101.67 ± 29.74	104.07 ± 2.40	97.22 ± 2.90	6.53 ± 0.03	2.05 ± 0.27
C4	0.13 ± 0.01	210.00 ± 20.00	76.20 ± 0.62	97.27 ± 2.69	6.74 ± 0.01	1.62 ± 0.48
C5	0.13 ± 0.01	118.67 ± 35.39	99.93 ± 7.23	106.48 ± 1.05	6.43 ± 0.01	1.45 ± 0.23
C6	0.21 ± 0.01	133.33 ± 25.66	120.17 ± 6.21	108.91 ± 1.11	6.16 ± 0.02	0.98 ± 0.15
C7	0.13 ± 0.01	181.33 ± 25.15	87.93 ± 2.08	108.19 ± 2.39	6.43 ± 0.02	2.15 ± 0.29
C8	0.16 ± 0.01	178.67 ± 30.07	103.77 ± 7.50	96.23 ± 1.08	6.61 ± 0.01	1.41 ± 0.18
C9	0.21 ± 0.01	122.00 ± 27.40	122.17 ± 1.75	100.46 ± 1.06	6.22 ± 0.02	1.18 ± 0.25

Uniformity of Drug Content

The drug content of the formulae A1–A9 ranged from 95.35 ± 1.37 to 108.12 ± 1.22% while the formulae C1–C9 were found to be in the range of 96.23 ± 1.08 to 108.91 ± 1.11% as shown in Tables 7 and 8. All formulae had drug content in the range of 90 to 110% of the limit given in the USP [33], which indicated the uniform and even distribution of the drug.

Scanning Electron Microscopy (SEM)

The SEM images showed that pure drug appears as irregular rod-like-shaped particles as shown in Fig. 5, whereas the SEM image of the optimized film and its cross-sectional image indicated that rough surfaces were observed due to the presence of irregular rod-like-shaped drug particles that were distributed uniformly throughout the film without any aggregation (Fig. 5) [30].

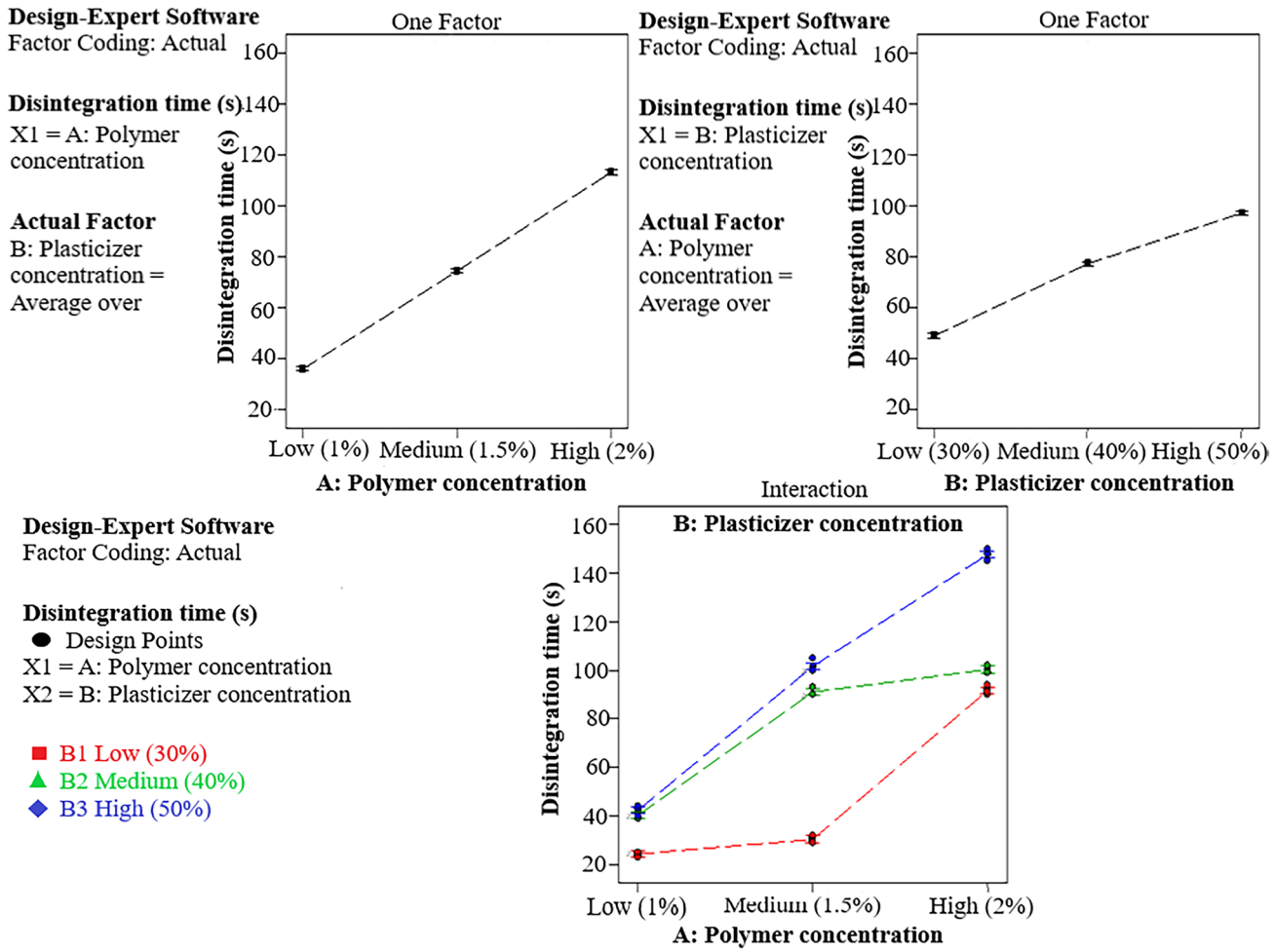

Fig. 5 Effect of formulation variables on the disintegration time of RT-ODFs using CMC polymer

Table 9 Effect of storage on the properties of the optimized formulae. Data represent the mean value ± SD ($n = 3$)

Parameter	Fresh A1	Stored A1	Fresh C1	Stored C1
I. Physical stability				
Appearance	No change in color and elasticity			
Disintegration time (s)	20.00 ± 2.00	22.00 ± 1.00	24.33 ± 1.16	23.00 ± 2.00
Weight variation (mg)	74.10 ± 0.56	75.58 ± 1.20	81.17 ± 7.22	83.34 ± 5.80
II. Chemical stability				
Drug content (%)	104.52 ± 1.23	102.00 ± 1.20	104.37 ± 2.00	101.20 ± 1.60
Q10 min (%)	97.12 ± 2.01	92.78 ± 2.00	85.09 ± 4.93	76.28 ± 3.40

Stability Studies

The results of stability studies of the optimized RT-ODFs for 90 days are summarized in Table 9. The optimized formulae A1 and C1 showed no significant variation in weight, disintegration time, drug content, and the amount of drug released after 10 min (Q10 min), indicating good physicochemical stability.

Determination of Pharmacokinetic Parameters in Rabbits

RT was analyzed by applying a validated HPLC method using a fluorescence detector to detect small amounts of the drug in plasma samples. For the pharmacokinetic study, the plasma concentration–time profile of RT following oral administration of RT-ODFs (A1) and the reference product

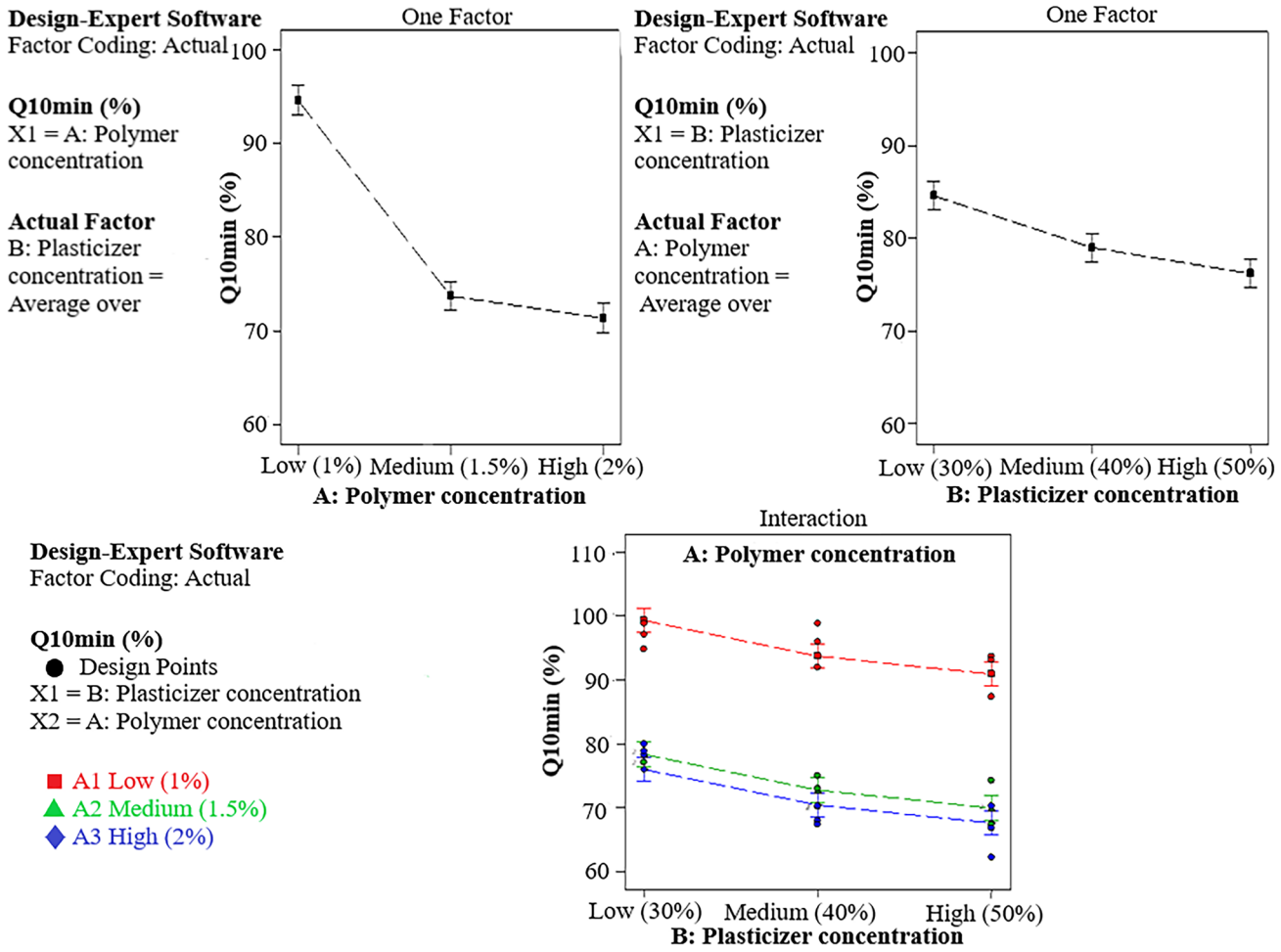

Fig. 6 Effect of formulation variables on the Q10 min of RT-ODFs using ALG-Na polymer

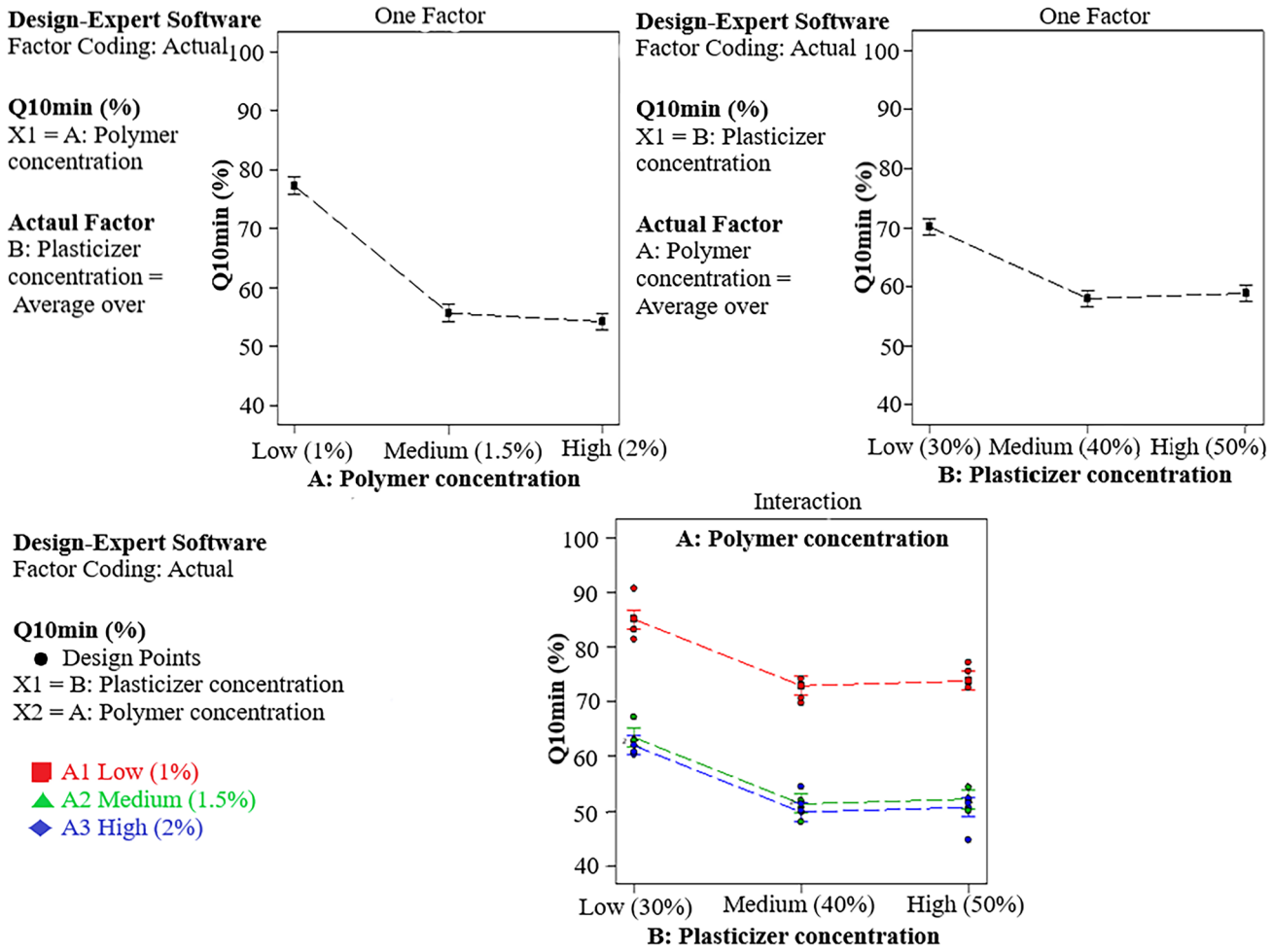

Fig. 7 Effect of formulation variables on the Q10 min of RT-ODFs using CMC polymer

(Exelon® capsule) is shown in Figs. 6 and 7. Pharmacokinetic parameters including C_{max}, T_{max}, AUC_{0-6}, $AUC_{0-\infty}$, $t_{1/2}$, MRT, and Ke are depicted in Table 10.

The results clearly showed a significant increase ($p < 0.0001$) in the mean C_{max} (177.99 ± 25.35 ng/mL) and $AUC_{0-\infty}$ values (283.97 ± 42.50 ng h/mL) after oral administration of RT-ODF achieving a higher rate and extent of drug absorption than the mean C_{max} (53.48 ± 2.84 ng/mL) and the $AUC_{0-\infty}$ values (148.50 ± 9.40 ng h/mL) of the reference product (Exelon® capsule) (Fig. 8).

Similarly, the T_{max} and MRT values of the RT-ODF showed a significant variation when compared to the reference product (Exelon® capsule) ($p < 0.0001$), indicating that the various dosage forms had different impacts on the maximum time needed for the drug to reach the maximum concentration as well as its residence time in the body.

The pharmacokinetic study revealed that the RT-ODFs modified the pharmacokinetic profile of the drug. The drug was more rapidly absorbed from the fast-dissolving films and achieved higher plasma concentration in a short interval after dosing, increasing the bioavailability by 1.91-fold relative to that of the reference oral capsule (Fig. 9). This might be due to the large exposed surface area of the film allowing fast disintegration and instant release of the drug. Moreover, the absorption of a fraction of the drug across the oral mucosa might bypass the first-pass hepatic metabolism and promote bioavailability.

Table 10 Pharmacokinetics of RT-ODFs (A1) and Exelon® following oral administration. Data represent the mean value ± SD ($n = 6$)

Pharmacokinetic parameters	RT-ODF (A1)	Exelon®
C_{max} (ng/mL)	177.99 ± 25.35	53.48 ± 2.84
T_{max} (h)	0.17 ± 0.00	0.25 ± 0.00
AUC_{0-6} (ng h/mL)	245.27 ± 26.21	109.97 ± 7.23
$AUC_{0-\infty}$ (ng h/mL)	283.97 ± 42.50	148.50 ± 9.40
$t_{1/2}$ (h)	2.38 ± 0.45	3.28 ± 0.08
MRT (h)	2.70 ± 0.38	4.32 ± 0.10
Ke (h^{-1})	0.30 ± 0.06	0.21 ± 0.00

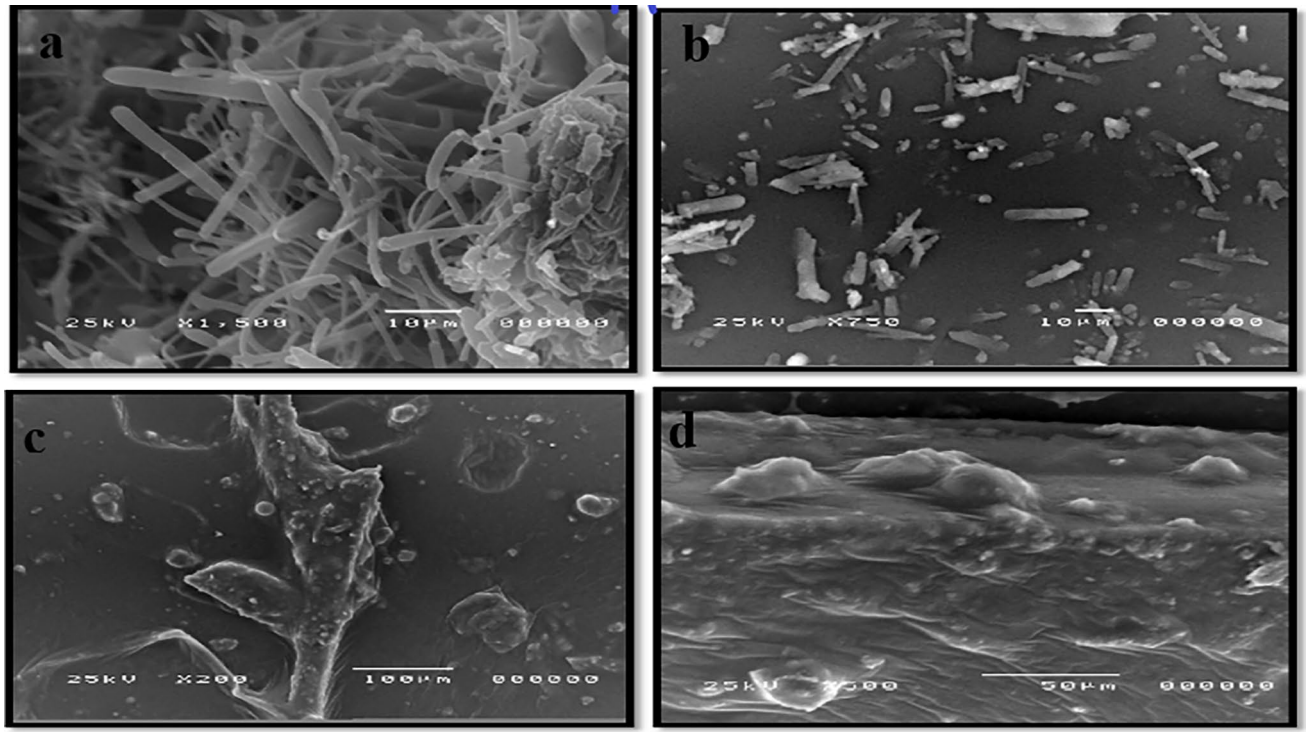

Fig. 8 Scanning electron micrographs of **a** pure rivastigmine tartrate (RT), **b**, **c** RT-ODF, and **d** its cross-sectional image

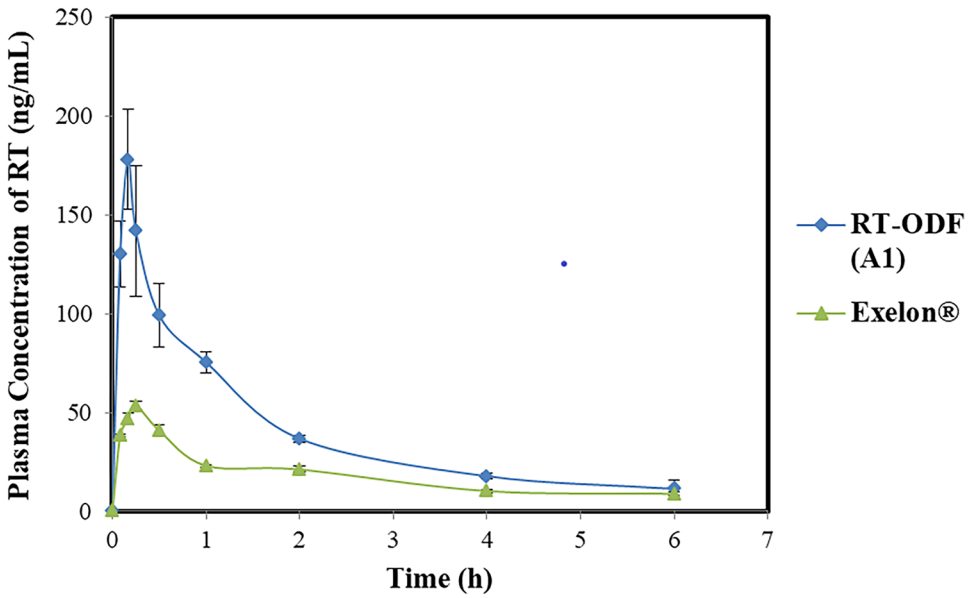

Fig. 9 Time versus mean plasma concentration profiles of RT following oral administration of RT-ODFs (A1) and Exelon.® in rabbits ($n=6$)

Conclusion

In this study, the RT-ODFs were well developed using ALG-Na and CMC as film-forming polymers and plasticized with glycerol. The physicomechanical properties of the formulae including the tensile strength (TS) in addition to the disintegration time were affected by the concentration of polymer and plasticizer. The optimized formula showed excellent mechanical properties, short disintegration time, and high dissolution. The higher values of pharmacokinetic parameters indicated the superiority of fast-dissolving oral films in the enhancement of the

bioavailability of the drug. The large surface area of the film, the fast disintegration of the film, and the enhanced drug dissolution in the oral cavity were the reasons for promoting bioavailability. In conclusion, RT-ODFs could potentially introduce a fast and easily administered dosage form for the treatment of dementia, providing improved patient compliance.

Ethics Approval

The experimental procedure and the in vivo study protocol were reviewed and approved by the Research Ethics Committee (REC) at the Faculty of Pharmacy, Cairo University, Egypt, on 29 October 2018 (REC Approval No. is PI (2286)).

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Data Availability The data that support the findings of this study are available from the corresponding author, [D.A.F.], upon reasonable request.

Declarations

Conflict of Interest The authors declare no competing interests.

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