Doi.org/10.36721/PJPS.2024.37.6.REG.1615-1624.1

Novel extended-release carbamazepine oral suspension: Formulation, evaluation and drug-release kinetic study

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Abstract: Common dosage forms have a number of drawbacks, including, but not exclusive, glitches in effectiveness, fluctuations in drug plasma concentration and poor patient's compliance. Such problems can be overcome by formulation of the drug as modified-release dosage forms. Usually, modified-release dosage forms are solid dosage form which are not proper for paediatrics and geriatrics. This research attempts to formulate and evaluate an extended-release carbamazepine oral suspension for paediatrics and geriatrics. Different ratios of Eudragit-L100 (Eud.) and PEG 4000 were used for encapsulation of carbamazepine powder. The selection of the best ratio was determined by dissolution test and FT-IR. The formulated ER suspensions were evaluated for organoleptic properties, pH, relative viscosity, density, sedimentation time, drug content and dissolution test. Additionally, drug release kinetics was studied to determine the possible mechanism of drug release. The best encapsulation ratio was (50:500:1000) PEG: Eud: Carbamazepine. Accordingly, formula 3 (F3) was selected. The evaluation tests showed an acceptable result. Mathematical analysis revealed that drug release kinetics following two kinetic models i.e. Hixson-Crowell and first-order model. The obtained results were encouraged to the possibility for manufacturing of first extended-release carbamazepine oral suspension. More in deep pre-clinical and clinical studies, in addition to production scale-up, are crucial.

Keywords: Carbamazepine, encapsulation, dissolution test, extended-release, Eudragit-L100.

Submitted on 08-11-2023 – Revised on 13-03-2024 – Accepted on 20-06-2024

INTRODUCTION

It is more imperative than ever to be aware of the steady pharmaceutical activity and lowering of the possible side effects of administered drugs. Dosage form design is an essential step in ensuring a safe and effective drug. Currently, most available drug dosage forms are designed to provide fast or immediate release of medication, but there are situations in which it would be advantageous to deliver a drug more slowly to the patient over time. In these cases, a modified-release dosage form would be ideal. The United States Pharmacopeia (USP) characterizes a modified-release dosage form as "The drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms". This includes modification of the site and/or time of drug delivery.

Some drugs are effective if they are taken at a precise dose at particular times. Others must be taken regularly to ensure that the patient stays healthy. In both cases, an extended-release dosage form can be used to accurately deliver the desired amount of the drug to the patient at the right time.

Carbamazepine (fig. 1) is an antiepileptic and anticonvulsant drug classified by biopharmaceutics Classification System (BCS) as class II with low solubility and high permeability (Medina *et al*., 2014). It is an extremely weak base (pKa: 13.9) with four anhydrous polymorphs (Dongyue *et al.,* 2022). Being used for the treatment of chronic illnesses, drug plasma levels must be carefully controlled.

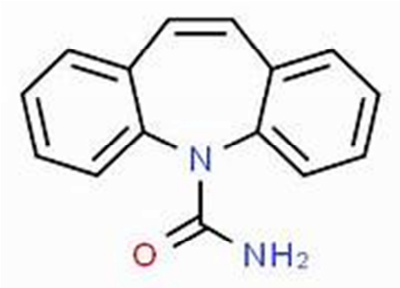

Fig. 1: Chemical structure of carbamazepine

The fluctuation in drug plasma level is the main cause of the drug's side effects and toxicity. To minimize such fluctuations, the drug may be formulated as a modified-release dosage form (Steffens and Wagner, 2020). Additionally, modified-release dosage forms prolong the lifespan of a drug, so, the dosage regimen may be reduced from 3 times per day to once or twice per day (He *et al.,* 2021). A reduction in dose frequency per day compared to a conventional dosage form is more patient compliance (Adepu and Ramakrishna, 2021).

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Using polymers, like Eudragits®, to encapsulate tablets, granules and powder is a broadly employed technique to provide on-site or time-controlled drug release. Eudragit L100 (a pH-dependent solubility polymer) is less liable to deterioration in an acidic medium and therefore is used as the enteric coating oral dosage form (Tokunaga *et al.,* 2021; Dongyue *et al.,* 2022). Usually, modified-release dosage forms are formulated as solid dosage forms like tablets and capsules. As these modified-release solid dosage forms are not suitable form paediatric and geriatric patients. There is no available modified-release oral liquid dosage form for treatment of certain chronic diseases like epilepsy. This first of its type oral suspension formulated for paediatric and geriatric patients with epilepsy and/or psychiatric who unable to use common modified-release solid dosage forms like tablets and capsules. To achieve both immediate and delayed drug release, coated and uncoated carbamazepine powder were used together in the formulation of extended-release oral suspension.

MATERIALS AND METHODS

Chemicals and reagents

Carbamazepine, Hydroxy propyl methyl cellulose (HPMC), Eudragit L100, Methyl paraben, Poly ethylene glycol 4000, Propyl paraben, Sorbic acid, Sorbitol and Saccharin sodium were a kind gift from the State Company for drug and medical supplies industry (SDI), Samarra-Iraq. Carbamazepine RS (Sigma-Aldrich, MO-USA); Kollidon 90F and Kollidon CL-M (BASF-Germany).

Instruments and Equipment

Dissolution tester PT-DT7 (Pharma-Germany); FT-IR (Shimadzu 1800, Japan); HPLC equipped with a double LC-20AD pump, SPD-20A UV-Visible detector (Shimadzu Inc.-Japan); Sensitive balance 4 digits XB220A (Presiza-Germany); Olympus microscope (Magnus Ch20i, Japan); Particle size analyser-Mastersizer 2000 (Malvern Panalytical, UK); Ostwald's capillary Viscometer; Portable Stainless Steel Homogenizer (Biobase-China); pH meter, Inolab 7110 (Germany); Ultraviolet-visible double beam spectrophotometer (Shimadzu Inc.-Japan).

Encapsulation of carbamazepine powder

Eudragit L100 with/without poly ethylene glycol 4000 (PEG4000) was used for the encapsulation of carbamazepine fine powder. Different ratios of Eudragit L100 only and PEG4000 and Eudragit as coating agents (table 1) were prepared and evaluated.

For Eudragit L100, solutions of concentrations 200mg/ 5 mL, 300mg/5mL, 400mg/5mL and 500/5mL were prepared by dissolving 400, 600, 800 and 1000mg of Eudragit L100 respectively in 3mL absolute ethanol, then completing the volume to 10mL with 1M NaOH. For PEG 4000, a solution of 10mg/mL was prepared by dissolving 500 mg PEG4000 in 50mL distilled water.

For encapsulation of carbamazepine with Eudragit L100 only, 1 g of carbamazepine powder was suspended in 5 mL of each of Eudragit L100 solutions of various concentrations, sonicated for 1 minute to ensure disaggregation of aggregated particles and coating of all particle's surfaces, spread over a glass petri dish, then transfer to the drying oven at 40°C for drying. After complete drying, the mass was ground with mortar and sieved using a US mesh screen 60 (particle size ≈ 250 microns).

For encapsulation of carbamazepine powder with PEG 4000 and Eudragit L100, 1g of carbamazepine was first suspended in 5mL of 10mg/mL PEG4000 solution, sonicated, for 2 minutes, spread over a glass petri dish, then transfer to the drying oven at 40°C for drying. After completely dried, the mass was ground with mortar, and sieved using a US mesh screen 60 (particle size ≈ 250 microns). The collected particles were suspended in 5 mL of each Eudragit L100 solutions of various concentrations, sonicated for 1-2 minutes to ensure disaggregation of aggregated particles and coating of all particle's surfaces, spread over a glass petri dish, then transfer to drying oven at 40°C for drying. After complete drying, the mass was ground with mortar, and sieved using a US mesh screen 60 (particle size ≈ 250 microns). The selection of the best encapsulation ratio is mainly based on the drug dissolution test in acidic medium. The solubility of raw carbamazepine powder is much higher than that for encapsulated carbamazepine powder as the solubility of Eudragit L100 is a pH- dependent.

Evaluation of the prepared encapsulated carbamazepine powder

The efficiency of encapsulation was evaluated depending on the dissolution behaviour of the encapsulated carbamazepine powder. The dissolution parameters were chosen as described by Dongyue *et al*., 2022 with minor modifications. The United States Pharmacopeia (USP) dissolution apparatus II (paddle method) was used with a paddle speed of 50 rpm; two dissolution buffers, i.e. pH 1.2 and pH 6.8, of 900mL each and temperature at 37◦C with maintaining of sink condition. Aliquots of 3mL were collected and filtered with 0.45µm nylon filter at fixed time points and replaced with a 3mL pre-heated fresh buffer. The samples were measured using a UV-vis spectrophotometer at 284 nm. The results were presented as % drug release against time.

FT-IR of encapsulated carbamazepine powder

The FT-IR spectra of carbamazepine powder, Eudragit L100, PEG 4000 and a physical mixture were tested. A dried pure KBr powder was used to prepare a disk of the under evaluated sample. The scan was achieved at a resolution of $2cm^{-1}$, with a range from 4000 to $400cm^{-1}$.

Preparation of extended-release (ER) oral suspension

Kollidon 90 F, Kollidon CL-M and HPMC were used as suspending agents. A variety of HPMC quantities were

tested. Other excipients including preservatives, sweetener and pH adjustment reagents were also used (table 2). The suspending medium was prepared by suspending the designed quantities of Kollidon 90 F, Kollidon CL-M and HPMC first in 10g of propylene glycol, adding 25mL deionised water, mixing, then adding 8 g of sorbitol solution and homogenised. In a 25 mL portion of deionised water, the desired quantity of sorbic acid, methyl paraben, propyl paraben, and saccharin sodium were dissolved, transferred to the prepared mixture of suspending agents and homogenised. A third portion of deionised water was added to the prepared suspension medium and homogenised. The prepared suspension medium was transferred to a graduate cylinder and the volume was completed to 100 mL with deionised water and homogenised. A mixture of 1-to-1.55 of carbamazepine fine mesh screen 60 and mixed well. A proportional addition of carbamazepine mixture was added to 70mL of suspending medium with continuous mixing using bench top homogeniser at 200 rpm, then after, the volume was completed to 100mL with suspension medium and homogenised at 1000 rpm. The prepared Carbamazepine suspension (100mg/5mL) was evaluated based on dissolution behaviour to select the best formula.

Organoleptic properties of the prepared suspension

The characteristic features of the prepared carbamazepine ER suspension including colour, odour, taste and texture were determined. Additionally, properties like relative viscosity, density, particle size distribution, sedimentation time in addition to assay were also evaluated.

For density, a 50mL graduated cylinder was weighed empty and weighed again after filled with the sample. The difference in weight represents the weight of sample. The density was calculated using the equation:

$$\text{Density (p)} = \frac{\text{weight}}{\text{volume}}$$

For relative viscosity, Ostwald's viscometer was used to measure the relative viscosity as described by Kestin *et al*., 1978. Both, density and viscosity were measured at the same room temperature (25±2°C). The drug content was determined as recommended by USP 41- NF 36 for assay of Carbamazepine extended-release tablets.

Drug release profile of the prepared suspension

The four prepared 2% Carbamazepine ER oral suspensions were evaluated for their dissolution behaviour using parameters described by USP41-NF36 for dissolution test of Carbamazepine extended-release tablets with minor modification of revolution speed.

Drug release kinetics

Data collected from dissolution tests were also used to delineate the drug release kinetics. Four mathematical model-dependent kinetics were used for assessing the release kinetics. These models are zero-order model, first-order model, Hixon-Crowell model, and Higuchi model. The highest value of the correlation coefficient (R^2) of the linear regression reveals which model the drug release follows (Askarizadeh *et al.,* 22023). As there is no reference product, model-independent drug release kinetic is not applicable here.

Stability studies

Stability studies are an authoritative step for certifying the quality of a product. These assessment tests aims to determine the shelf-life of a product. Additionally, it is useful for evaluating the behaviour of a product during storage; assessing the effect (s) of environmental conditions, such as temperature and humidity, on the product; and selecting the finest storage conditions. Parameters like temperature and relative humidity, were selected based on the climatic zone classification of the ICH-Q1A (R2) tripartite guideline (2005) and ASEAN guideline (2005). ASEAN countries, including Iraq, were classified as zone III (hot and dry region). As stated in the ICH-Q1A (R2) guideline (2005), long term stability studies should be conducted under the conditions of 30°C ±2°C and 35% RH ±5% RH for 12 months. Sampling was at 3 months interval for assaying of drug contain, in addition to evaluation of parameters like appearance, colour, odour, texture, relative viscosity and pH.

STATISTICAL ANALYSIS

Mean dissolution time ± SEM (N=6) was determined using SPSS software (Version 24.0). In order to evaluate the dug release kinetics of carbamazepine, dissolution data were fitted to different kinetic models: are Zero-order model, First-order model, Hixon-Crowell model, and Higuchi model. The model with the highest determination coefficient was chosen as the best fit. Data analysis was carried out using the Excel add-in DDSolver program.

RESULTS

Evaluation of the prepared encapsulated carbamazepine powder

The selection of best encapsulation composition and ratio was reliant on the graphical analysis of carbamazepine release from the encapsulated particles in two dissolution medium, i.e. pH 1.2 and pH 6.8 (fig. 2). Generally, encapsulation of carbamazepine powder leads to decreased solubility in an acidic medium. This means that the encapsulation of carbamazepine with a pH-dependent solubility polymer like Eudragit L100 will prevent the drug from dissolving in the acidic medium of the stomach and will pass to the next part of gastrointestinal tract.

This pH-dependent solubility provides the desired delayed drug release that will also offer the extended drug effect. Carbamazepine powder encapsulated with PEG 4000 and Eudragit L100 showed almost the same solubility in an acidic medium compared to that encapsulated with Eudragit L100 alone.

Table 1: Ratios of encapsulation materials to carbamazepine powder

Eudragit L100 : Carbamazepine (mg : mg)			
Eud 1	Eud2	Eud3	Eud4
200 : 1000	300 : 1000	400 : 1000	500 : 1000
PEG 4000 : Eudragit L100 : Carbamazepine (mg : mg : mg)			
PEG4000+ Eud1	PEG4000+ Eud2	PEG4000 + Eud3	PEG4000+ Eud4
50 : 200: 1000	50 : 300: 1000	50 : 400 : 1000	50 : 500: 1000

Table 2: Constituents of four prepared extended release carbamazepine oral suspension

Material	Role	F1 (g)	F2 (g)	F3 (g)	F4 (g)
Carbamazepine	API	2	2	2	2
propylene glycol	Stabilizer and co-solvent	10	10	10	10
Kollidon 90 F	Suspending agent	0.2	0.2	0.2	0.2
Kollidon CL-M	Suspending agent	0.3	0.3	0.3	0.3
HPMC	Suspending agent, crystalline growth inhibitor	2	3	4	5
Sorbitol solution	sweetener and provide texture to products	8	8	8	8
Sorbic acid	pH control	0.08	0.08	0.08	0.08
Methyl paraben	Preservative	0.5	0.5	0.5	0.5
Propyl paraben	Preservative	0.15	0.15	0.15	0.15
Saccharin sodium	Sweetener	0.1	0.1	0.1	0.1
Deionized Water		Q.S. 100mL	Q.S. 100mL	Q.S. 100mL	Q.S. 100mL

Table 3: Some parameters for the prepared encapsulated carbamazepine ER oral suspension

Parameter	F1	F2	F3	F4
pH	4.63	4.71	4.78	4.92
Density (g/mL)	1.0688	1.0693	1.0708	1.0713
Relative viscosity (Pa.S)	0.01646	0.01663	0.01745	0.01848
Sedimentation time	> 16 hs	> 16 hs	> 20 hs	> 20 hs
Assay (%)	97.43	95.82	99.28	95.77

Table 4: The results of four mathematical model-dependent kinetic for formula 3

Mathematical model	Equation	Correlation coefficient (R^2)
Zero-order	y = 2.5668x + 46.932	0.5839
First-order	y = -2.5668x + 53.068	0.8739
Higuchi model	y = 17.589x + 23.387	0.6460
Hixson-Crowell model	y = -0.1061x + 3.7765	0.8787

Table 5: Organoleptic characteristics and percent drug content changes for the prepared carbamazepine ER suspension stored in long-term stability conditions

Parameter	Initial	3 months	6 months	9 months	12 months
Appearance	A creamy white colour suspension	NOC	NOC	NOC	NOC
Odour	No characteristic odour	NOC	NOC	NOC	NOC
Taste	Slightly sweet	NOC	NOC	NOC	NOC
Relative viscosity (Pa.S)	0.01744	0.01747	0.01751	0.01753	0.01753
pH	4.76	4.72	4.72	4.69	4.71
Drug content (mg/5 mL)	99.28	99.124	98.345	97.121	96.481

NOC: no observed change

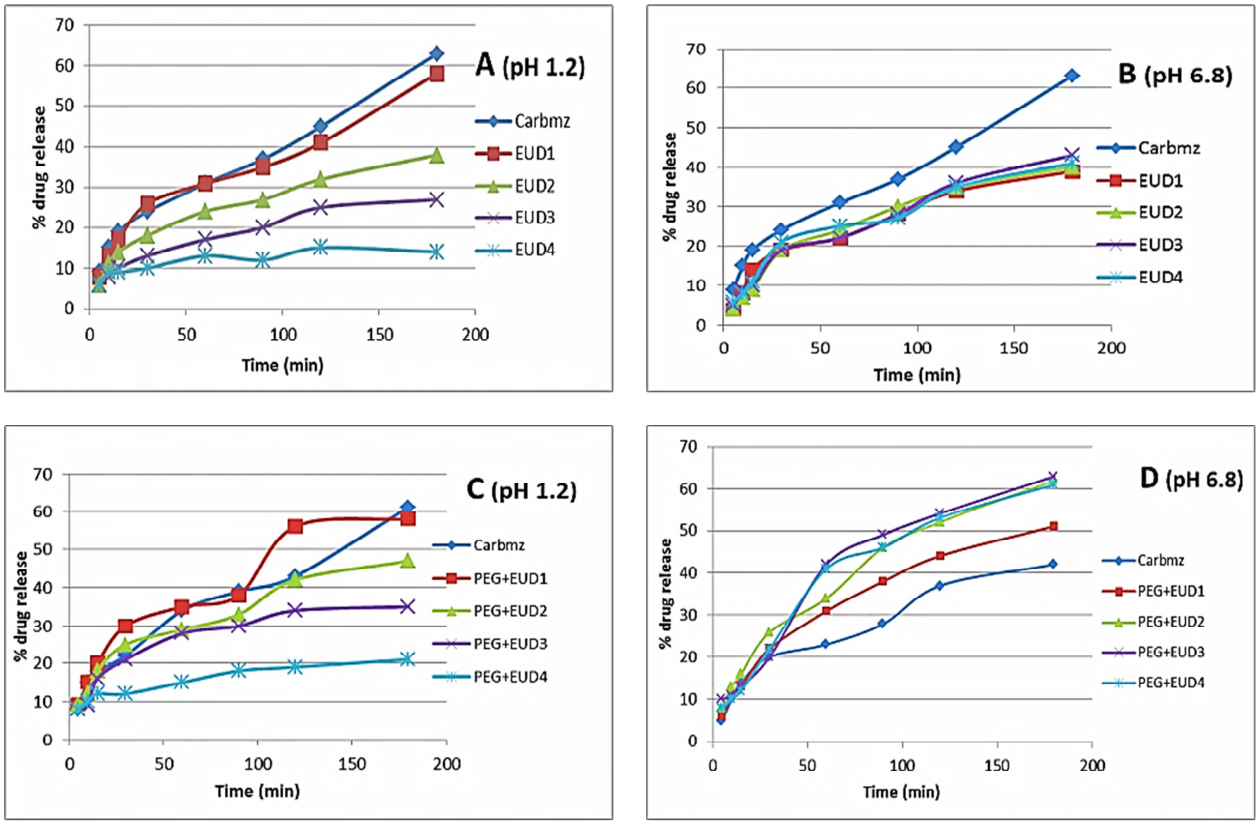

Fig. 2: Dissolution test for the prepared encapsulated carbamazepine powder. A: % drug release of carbamazepine encapsulated with Eudragit L100 at pH 1.2 dissolution medium; B: % drug release of carbamazepine encapsulated with Eudragit L100 at pH 6.8 dissolution medium; C: % drug release of carbamazepine encapsulated with PEG 4000 and Eudragit at pH 1.2 dissolution medium; and D: % drug release of carbamazepine encapsulated with PEG 4000 and Eudragit at pH 6.8 dissolution medium.

The solubility of powder encapsulated with PEG 4000 and Eudragit L100 in pH 6.8 medium appears to be improved compared to raw carbamazepine powder and that encapsulated with Eudragit L100 alone. Accordingly, encapsulation of carbamazepine powder with PEG4000: Eudragit L100 (ratio 50:500:1000) mentioned in table 1 as (PEG4000 + Eud4) was selected for preparation of ER carbamazepine suspension.

FT-IR for encapsulated carbamazepine powder

A comparison of the FT-IR spectra of carbamazepine powder, Eudragit L100, PEG 4000 and physical mixture of (fig. 3) revealed no appearance of new additional peaks, disappearance or shifts of characteristic peaks. This result approves the compatibility of used materials and the absence of any chemical or physical interaction between carbamazepine and the used polymers.

Organoleptic properties of the prepared encapsulated carbamazepine ER suspension

A creamy white colour suspension, sweet taste, no characteristic odour with a smooth texture. table 3 shows some parameters including pH, density, relative viscosity, and sedimentation time in addition to assay. All four prepared encapsulated carbamazepine ER suspensions showed acceptable values specially for pH, sedimentation time and assay.

Drug release profile of the prepared suspension

The results of the dissolution test for the four formulated 2% carbamazepine ER suspensions were conducted as designated by USP41-NF36 for the dissolution test of Carbamazepine extended-release tablets Dissolution test 1. A minor modification on the number of samples drawn to be 1, 2, 3, 4, 6, 12 and 24h and revolution per minutes to be 50 rpm. The four formulas showed drug release at hour 3 higher than the USP acceptance criterion (fig. 4). All the formulas showed initial burst cumulative drug release at hour 3 ranging from 36% to 58% followed by steady extended cumulative release up to hour 24 ranging from 71% to 96%.

Microscopic images and particle size analysis

Microscopic imaging is a simple and useful method for the examination of the morphological changes that occurred to carbamazepine particles after encapsulation (fig. 5). Also, it gives sight into encapsulation efficiency. Moreover, the size of suspended particle was measured using Mastersizer® 2000 to determine particle size distribution.

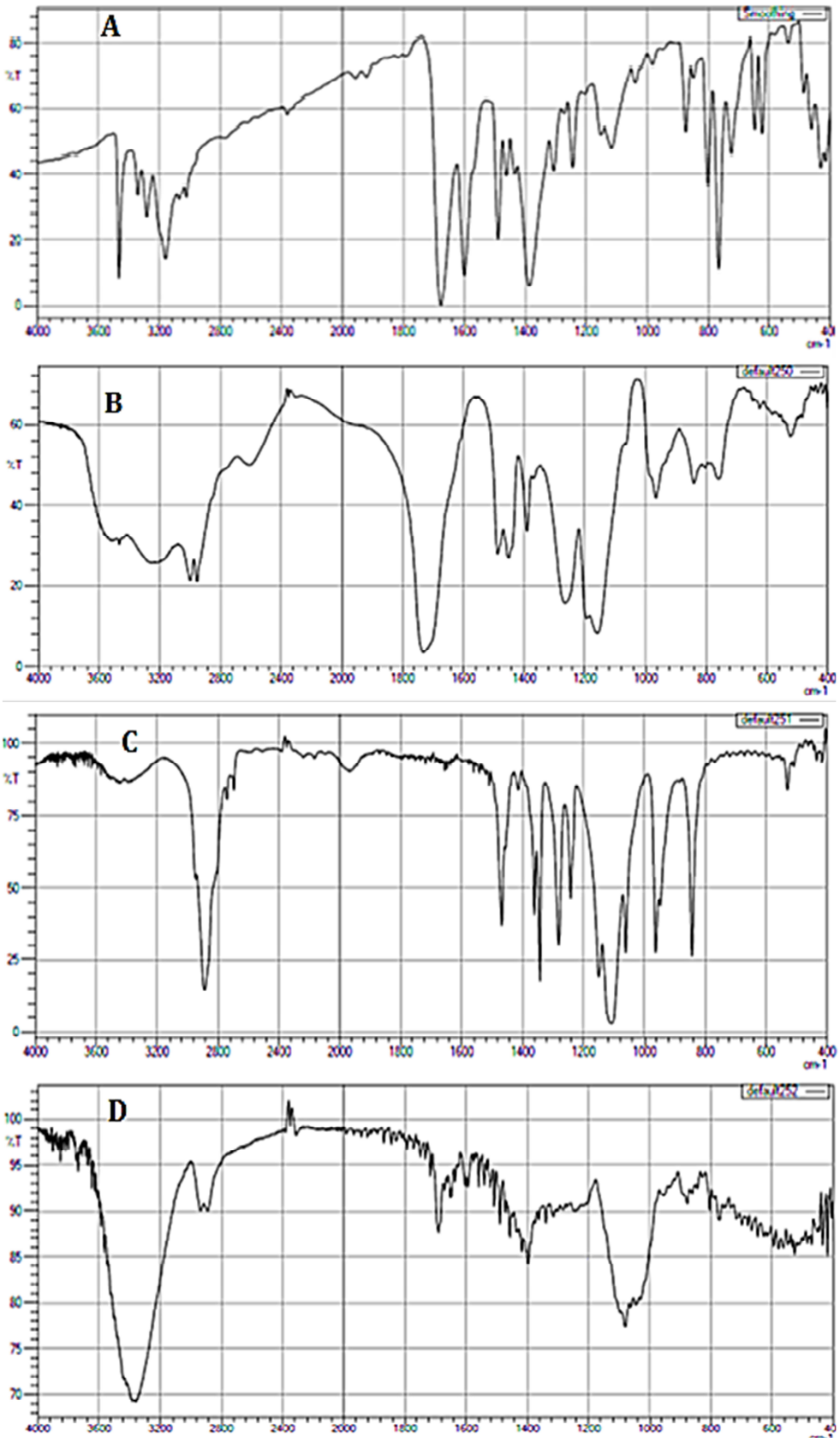

Fig. 3: FT-IR spectra for A: carbamazepine powder, B: Eudragit L100, C: PEG 4000 and D: physical mixture.

The images illustrated that some carbamazepine particles were not completely encapsulated with the coating materials. This may be due to manual bench technique in addition to grinding and screening of the encapsulated particles.

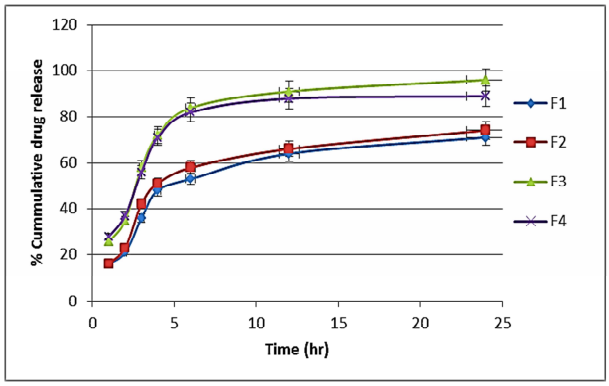

Fig. 4: Comparison of the *drug release profile* of the four prepared encapsulated carbamazepine ER oral suspension.

A more efficient encapsulation technique like a fluidized bed may be considered for better encapsulation and production scale-up. Fig. 6 shows the particle size distribution of suspended particles in Carbamazepine ER suspension formula 3. The mean particle size was 203.3 µm.

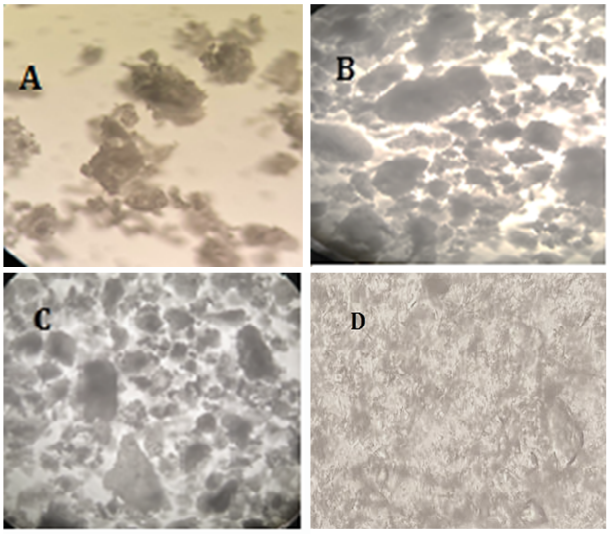

Fig. 5: A microscopic imaging for: A: raw carbamazepine powder; B: encapsulated carbamazepine powder (PEG-Eudr3); C: Physical mixture of F3; and D: prepared carbamazepine ER suspension (F3).

Drug release kinetics

Mathematical kinetic models are an important tool for understanding the mechanism of drug release from the dosage form. It discloses the effects of the formulation and excipients on the drug's dissolution behaviour. Additionally, drug release kinetic data can be useful in predicting the *in vivo* performance of the oral dosage form.

Employing the results obtained from the dissolution test, *in vitro* drug release kinetic was predicted. Showing the highest correlation coefficient, Hixson-Crowell model exhibited the most possible fitting mathematical model (table 4). This means that the drug release process occurs through a simple dissolution of the drug from the surface of the particles. In another word, the dissolution process here is controlled by the surface area that comes in contact with the dissolution medium, and particle size as a function of time.

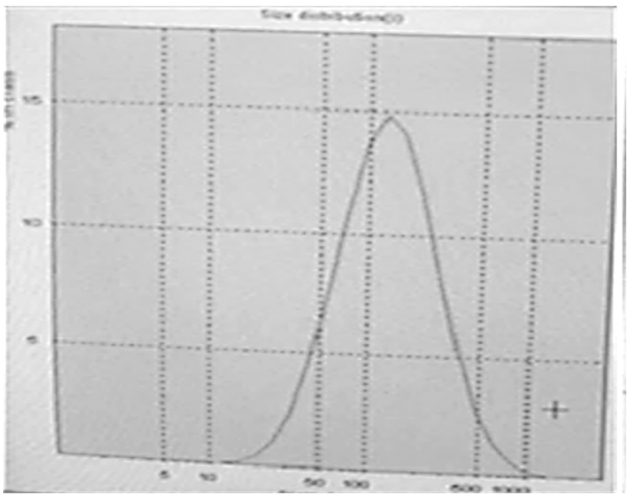

Fig. 6: Particle size distribution of the prepared ER carbamazepine oral suspension.

The second highest mathematical model was first-order kinetic, so, the drug release rate was controlled by surface area and proportional to the concentration of the drug in the dissolution medium. In first order kinetic dissolving of the drug started immediately after sinking the dosage form into the dissolution medium; so called the 'burst effect' (Gouda *et al.,* 2017).

Stability studies

A long-term stability study was conducted for 12 months at 30±2°C and 35%±5% RH with testing frequencies of 0, 3, 6, 9 and 12 months. The samples of formulated ER carbamazepine suspension were stored in separated aliquots for each testing frequency to avoid unnecessary exposure of the sample to air and humidity. At each testing frequency, the sample was evaluated for drug contain, in addition to evaluation of parameters like appearance, colour, odour, texture, relative viscosity and pH.

No noticeable changes were observed in the appearance, odour, taste, relative viscosity and pH after stored for 12 months under long-term stability conditions (table 5).

Regression line intersects the lower acceptable limit (90% drug content) is considered the shelf life (fig. 7). The estimated shelf life for prepared carbamazepine ER oral suspension was found to be 30 months.

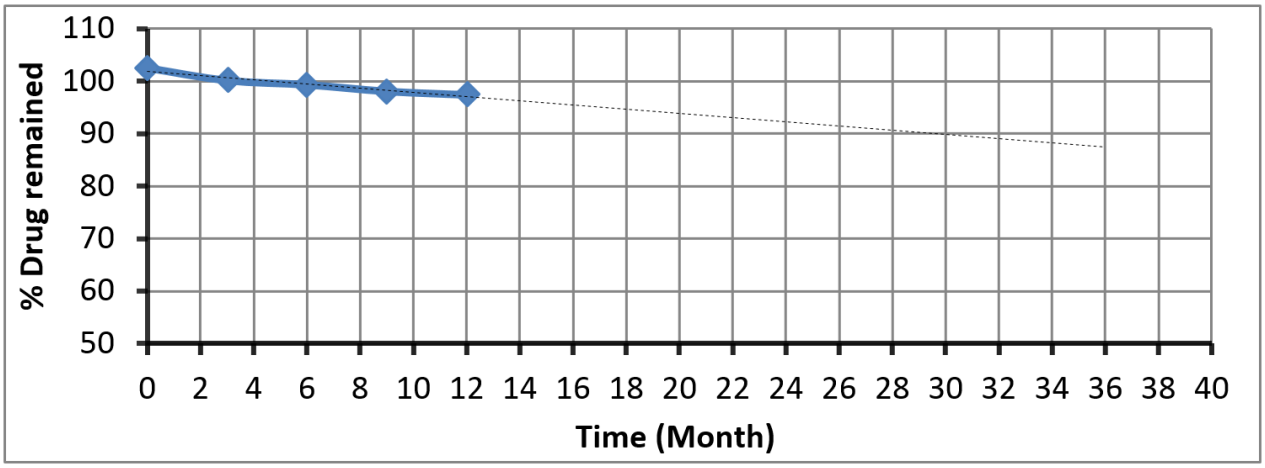

Fig. 7: Regression line of drug content (%) against time (month) of Carbamazepine in prepared carbamazepine ER suspension stored in long-term stability conditions.

DISCUSSION

As stated by USP, the characteristics of a modified drug release system is "The drug release characteristics of time, course and/or location". This includes technologies that modify the site of drug release and delivery. For drugs like carbamazepine which rapidly metabolized in the younger age groups than in adults (Tolou-Ghamari *et al.,* 2013), a modified release dosage form seems to be useful. Extended-release dosage forms prolong the plasma steady state of a drug over an extended time so that dosage regimen minimizes from 3 times a day to just once or twice a day. These types of dosage forms can also prevent a sudden increase in drug concentration within a patient's body which can lead to harmful side effects. For example, Carbamazepine extended-release tablets given once /day afford a steady-state plasma level comparable to a 3 times/day dosage regimen, conventional carbamazepine oral suspension with a plasma peak at approximately 3 to 12 hours compared to 1.5 hours (Mayo Clinic, 2022). The results of *in vitro* drug dissolution and drug release kinetics shows that the prepared carbamazepine ER oral suspension has a steady and prolonged drug release pattern.

As it is a hydrophilic solubilizing agent, PEGs are often used to improve the dissolution and solubility of poorly water-soluble drugs such as carbamazepine (Bolourchiana *et al.,* 2013). PEG can enhance the dissolution rate of carbamazepine by reducing the boundary layer resistance that hinders the diffusion of drug molecules from the solid surface into the bulk solution (Shamma *et al.,* 2016). Patra *et al*. (2023) utilized and mentioned the solubility improvement effects of PEGs. The solubility of PEG 4000 can be affected by pH, but the exact effects will depend on the pH of the solution and the concentration of PEG 4000. At neutral pH (around pH 7), PEG 4000 is highly soluble in water and many other solvents. As the pH of the solution becomes more acidic or basic, the solubility of PEG 4000 can decrease. At low pH values (acidic conditions), the carboxylic groups on the PEG 4000 molecule can become protonated, resulting in a decrease in solubility. Conversely, at high pH values (basic conditions), the hydroxyl groups on the PEG 4000 molecule can become deprotonated, also resulting in a decrease in solubility (Ke *et al.,* 2023).

Eudragit is the trade name for group of copolymers derived from esters of acrylic and meth- acrylic acid in which its properties are determined by the functional groups. Eudragit L polymer enables a pH dependent drug release. From simple taste masking by resistance merely to gastric fluid feat up to controlled drug release in different parts of the gastrointestinal tract (Nandy and Gupta, 2014).

Being designed to have both immediate and delayed drug release, the prepared suspension contains 50% raw and 50% encapsulated carbamazepine power. Expectedly, the raw carbamazepine powder will quickly dissolve in the medium leading to an increase in the rate of dissolution higher than that of USP acceptance table 1 for carbamazepine extended-release tablets. The burst drug release was attributed to the solubility of the raw carbamazepine powder that adsorbed at the surface of the encapsulation film. However, the delayed drug release was due to slower process of solubility of Eudragit L100 by swelling and erosion (Mašková *et al.,* 2019) than after, the solubilisation of carbamazepine powder. Graphical analysis of fig. 4 illustrated that formula 3 (see table 2 above) shows the most acceptable drug release profile compared to other formulas.

Kim *et al.* 2020 successfully used PEG/Eudragit L100 to improve the pharmacokinetic properties of celecoxib. In addition to the improvement of physical and chemical properties, enhancement in the absorption and bioavailability of celecoxib was obtained. They attributed

the results due to enhanced dissolution behaviour due to the addition of solubilizer (PEG) and crystalline-growth inhibitor HPMC and Eudragit L100 (Alsammarraie *et al.,* 2021).

Obtaining two drug release mechanisms is simply expected as the prepared carbamazepine ER suspension formulated using two forms of carbamazepine, raw and encapsulated particles. Raw carbamazepine particles follow first-order kinetics, while encapsulated one follows Hixson-Crowell model. Drug release kinetic data are fundamental in predicting the *in vivo* performance of the oral dosage form. Several factors can affect the drug release kinetics, include factors related to the drug itself, such as particle size, solubility, crystallinity and polymorphism and factors related to dosage form, such as the drug: excipients ratio, type of excipient or polymer used, and miscibility of the drug in excipients (Paarakh *et al.,* 2018). Cetin *et al.,* 2010 found that diclofenac sodium release kinetic from particles coated with Eudragit L100 was fitting to first-order kinetics. They explain that Eudragit L100, as a pH-dependent solubility polymer, well swallowed and erodes when comes in contact with aqueous medium allowing the drug to be in contact with the medium and release the dissolved drug.

Long term stability studies estimated the shelf life of prepared ER carbanmazepine suspension to be about 30 months. For any common pharmaceutical product the shelf life is preferable to be more than two years to be commercially valuable.

CONCLUSION

As the prepared carbamazepine ER oral suspension showed an extended drug release pattern, it is expected to provide a prolonged drug plasma steady concentration. The results of the research raise the hope to manufacture a novel and the very first of its kind of extended-release carbamazepine oral suspension which is useful for paediatric and geriatric patients. Accordingly, a longer drug activity, a less side effects and more patient compliance are probable.

The above presented results are part of continuous work for production of ER carbamazepine oral suspension. Profounder pre-clinical and clinical studies about the bio-availability and bio-equivalency are highly recommended. Additionally, more studies of manufacturing scale-up are also required.

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