Research article

Mucoadhesive buccal tablets incorporating curcumin solid dispersion as a potential approach for enhancing curcumin therapeutic efficacy in oral inflammatory disorders

Heba MK Ebada [a], Maha MA.Nasra [b], Heba A Hazzah [c], Ossama Y Abdallah [b]

[a] Central Lab, Faculty of Pharmacy, Damanhour University, Damanhour, Egypt.

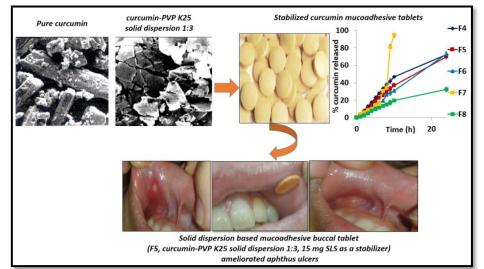[b] Department of Pharmaceutics, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.

[c] Department of Pharmaceutics, Faculty of Pharmacy and Dug Manufacturing, Pharos University, Alexandrioa, Egypt.

*Corresponding author: Central Lab, Faculty of Pharmacy, University of Damanhour. El Gomhouria Street, Damanhour Post Office, P.O.Box 22511, Damanhour, Egypt.

Phone: (+2) 01223444145   Fax: 00203 4873273

E-mail: heba.m.khiry@gmail.com, heba.ebada@pharm.dmu.edu.eg

Abstract:

Curcumin (cur) elicits a wide spectrum of potent responses for local treatment of oral disorders. However, its clinical use in the oral cavity is limited by its poor solubility and chemical instability at salivary pH. This study aims to develop cur mucoadhesive buccal

Solid dispersion based mucoadhesive buccal tablet
(F5, curcumin-PVP K25 solid dispersion 1:3, 15 mg SLS as a stabilizer)
ameliorated aphthus ulcers

tablet formulation with enhanced cur solubility and stability. For this purpose, a rapidly dissolving solid dispersion (SD) was developed using PVP (Kollidon®25). In addition, chemical stability in phosphate buffer saline (PBS) pH 6.8 was investigated for the first time using different stabilizers to ensure cur stability for in-vitro and in-vivo studies. After addressing solubility and stability challenges, buccal tablets formulations were developed using Hydroxypropyl methylcellulose (HPMC) and Carboxymethyl cellulose (CMC sodium) mixture in different ratios with or without SLS as stabilizer.

100

Tablets containing HPMC.K15M: CMC sodium (5:1), SD (1:3), and 15 mg SLS showed the best results regarding mucoadhesive strength, in-vivo residence time, and release rate profile and were considered as the optimized formulation. The optimized formulation ensured cur stability as well as a controlled release rate, with considerable cur levels in saliva for over 12h. Preliminary clinical evaluation showed remarkable anti-inflammatory and healing effects in patients with aphthous ulcer, concluding that cur stabilized mucoadhesive formulation can efficiently treat various inflammatory oral diseases.

Keywords: Curcumin, Mucoadhesive, Stability, Solubility, Buccal Delivery.

1. Introduction

Phytotherapy is regarded as a powerful alternative for addressing several human diseases [1]. Particular attention has been given to curcumin (cur) -the golden spice- a polyphenolic compound obtained from the pulp of Turmeric (haldi), a rhizome of Curcuma longa [2, 3]. The biological and medicinal properties of cur exhibit antioxidant, anti-inflammatory, antimicrobial [4], and anti-carcinogenic activities [5]. Cur also shows angiogenesis inhibition and neuroprotective properties [6-8]. Moreover, cur has been documented for treating several disorders in the oral site, such as Candida-related denture stomatitis and oropharyngeal candidiasis [9, 10], oral squamous cell carcinoma [11], dental pain [12, 13], and periodontal problems [14]. Despite its wide activities, its use is clinically restricted due to its low solubility in water, poor permeability, hydrolytic degradation in neutral and alkaline pH, and extensive metabolism.

Buccal administration has been recognized as the first therapeutic choice to target damaged buccal tissue, decreasing systemic side effects and potentiating the therapeutic efficacy with good patient compliance [15, 16]. However, this route exhibited various drawbacks such as rapid clearance connected to the continual mucus renewal and swallowing along with restricted surface area [17]. Given these constraints, an optimal buccal formulation should have the ability to stay in the buccal cavity for extended durations, enabling effective and regulated release.

Over the past few decades, intense researches were devoted to enhance cur bioavailability using different approaches, however, only a few studies were oriented to improve its physicochemical stability. Amorphization is a highly successful method for improving the solubility of pharmaceuticals with low solubility. As amorphous compounds have the potential to create an extremely supersaturated drug solution upon dissolution [18, 19]. Supersaturation occurs due to the existence of a weak energy barrier, which facilitates the dissolution of amorphous medications. This results in a significantly increased solubility of the drug compared to its crystalline form [20]. Several amorphous cur formulations with improved cur solubility have been created as amorphous solid dispersions [21-23], co-amorphous systems [24, 25], and amorphous nanoparticles [26, 27]. Amidst these various amorphous pharmacological formulations, the amorphous cur solid dispersion (Cur SD) is noteworthy for its notably uncomplicated technique of manufacture.

Cur SD was previously studied, however, only a few limited works addressed both in-vitro and in-vivo evaluation of SD [28-34]. Most studies just focused on one of the cur obstacles and skipped discussing the other, for instance, reporting increasing the solubility without referring to stability, or not reporting the stabilization during dissolution conditions [35, 36]. Chuah et al [29] reported the enhancement of cur bioavailability but did not mention the release testing of the SD. In addition, SD was

administered orally as a suspension containing 0.1% tween without explaining if the tween affects the enhancement of absorption or not [29].

Although cur/PVP solid dispersion has been created before [37, 38], the focus of both investigations was on improving solubility without considering the stability issue. Cur solid dispersion was prepared with PVP at 1:6 and 1:9 by Hernandez-Patlan, *et al.* [37] to evaluate its antibacterial efficacy against Salmonella Enteritidis. Without considering stability, they assessed the solubility of cur at various pH ranges (1.25–6.4). As a result, they stated that the solubility of cur at pH 6.4 could not be determined, and that cur SD enhanced solubility to range from 94.27 ± 4.7 to 212.82 ± 1.2 µg/mL. Meanwhile, Paradkar *et al* [38] developed solid dispersions of cur in different ratios with PVP by spray drying, and dissolution studies of cur and its solid dispersions were carried out in 0.1N HCl. Herein, the current study encompassed both solubility and stability studies either for in-vitro or in-vivo studies as it is crucial to incorporate the solubility-enhanced cur form into a mucoadhesive buccal system and maintain its stability to ensure its efficacy for the buccal route.

Therefore, the present study aimed to prepare extended-release cur buccal tablets using mucoadhesive hydrophilic polymers namely hydroxypropylmethylcellulose (HPMC), Sodium carboxymethylcellulose (NaCMC) to improve cur buccal availability as a significant advancement to surmount current challenges to attain a prospective localized treatment for many oral ailments. In this regard, a simple technique was addressed to overcome the two main challenging problems of cur, poor water solubility and hydrolytic degradation at salivary pH. Also, a simplified in-vitro dissolution test was adopted ensuring cur stability under experimental circumstances.

2. Methods
2.1. Materials
Curcumin powder (Hebei Food Additive Co., Ltd China), (purity > 95%).Sodium lauryl sulfate (SLS), Magnesium stearate and Mannitol, ADWIC, (El-Nasr Pharmaceutical Co., Egypt**.),** PEG-7-glyceryl cocoate (Galaxy surfactants (Galaxy, Navi, Mumbai, India), Polyvinylpyrrolidone (kollidon®25, PVPK-25) (Quzhou Jianhua Nanhang Industrial co, Ltd, China). Carboxymethylcelloluse sodium (CMC Na), (Simag chem. Corporation, China). Hydroxypropylmethylcellulose15000c.p, (HPMCK15M), (Methocel), (Colorcon co., USA.) All the other chemicals were of high analytical grade.

2.2. Solubility studies
Excess amount of cur was added to 5 mL PBS (pH 6.8) containing 0.5%SLS and different concentrations of HPMC K15M (0.2%, 0.5%, 1%), Pluronic 127 (2%, 4%, 6%, 8%) and PVP K-25 (2%, 4%, 6% and 8%) in amber glass vials. A thermostatically controlled water bath maintained at $37\pm0.1°C$ was used to shake vials for 24 h. Vials were then allowed to stand for another 24 h to reach equilibrium. A 0.45 µm pore size membrane filter was employed to filter the supernatants. Filtrates were appropriately diluted and analyzed spectrophotometrically at 421 nm for the determination of cur concentration. All experiments were done in triplicate.

2.3. Preparation of solid dispersion
Solid dispersions of Cur and PVP K-25 in different weight ratios (1:1, 1:2, 1:3, 1:5, and 1:8) were prepared using the solvent evaporation method. Cur and PVP K-25 were dissolved in a minimum amount of ethanol; the solvent was then evaporated over a boiling water bath with constant vigorous stirring to form a uniform solid mass. The obtained solid dispersion was desiccated for 24 h. Dispersions were then pulverized using a mortar and a pestle, passed through a 250-

μm sieve, and then kept in amber glass bottles in a desiccator at room temperature.

2.4. Physical and chemical evaluation of prepared solid dispersions

2.4.1. Fourier transform-infrared (FTIR)

FTIR spectra of cur, physical mixtures prepared by trituration method and SDs were obtained using a Perkin-Elmer spectrometer over a scanning range 450 to 4000 cm^{-1} and a resolution of 2 cm^{-1}.

2.4.2. Differential scanning calorimetry (DSC)

DSC analysis was accomplished using the Perkin Elmer Differential scanning calorimeter (DSC 6) (Perkin Elmer, Rodgau, Germany). A thin layer of selected sample (SD 1:3) was spread in aluminum pans under a nitrogen air atmosphere at a flow rate of 20 mL/min and heated and evaluated at 30°C to 300°C. The test was applied for solid dispersion in comparison to pure cur, and PVP K-25.

2.4.3. Powder X-ray diffraction (PXRD)

PXRD patterns of cur, SD1:3, SD1:5, and SD1:8 were recorded using X-ray diffractometer, (Philips PW 3710, Netherland) with CuKα radiation, collimated by a 0.08°divergence slit and a 0.2°receiving slit and scanned at a rate of 2.4°/min over the 2θ range of 5-50°.

2.4.4. Particle size and polydispersity index (PDI) analysis

Samples of different SD formulations were dispersed in distilled water- previously filtered- and appropriately diluted. The particle size and PDI were then evaluated by Malvern zetasizer (Malvern, UK).

2.4.5. Scanning electron microscopy (SEM)

Particle morphology of pure cur and selected formula (SD1:3) were examined by SEM topographic mode. Samples were dispersed directly on a double-sided tape and made conductive by coating with gold in the chamber of SEM (JSM 5300, JOEL, Japan),

and images were acquired using i-scan 2000 software.

2.4.6. Chemical stability studies and screening of stabilizers:

To test the chemical stability of cur as a pure drug and in prepared SD in the presence and absence of a stabilizer, Cur stock solution was prepared in acetone at a concentration of 500mg/mL, and was diluted properly with PBS (pH 6.8) to obtain a concentration of 10μg/mL. An amount of cur SD equivalent to 10μg/mL cur was also added to PBS (pH 6.8). The samples were filtered using 0.45 µm pore-sized filter and then filtrates were kept at 37 °C in a thermostatically controlled water bath. Samples were withdrawn at time intervals (0, 5, 10, 15, 20, 30, 40, 50, and 60 min) and analyzed spectrophotometrically at λ max of 421 nm [39, 40]. The concentration calculated at zero time was considered to be 100 %. The same procedure was repeated for cur SD with different concentrations of some surface active agents (SAA) namely SLS and PEG-7-glyceryl cocoate and non-surface active agents such as PVP K-25 and HPMC K15M to determine the appropriate stabilizer for cur and the minimum concentration capable of maintaining cur stability in saliva.

2.4.7. Solubility studies

The same procedure was repeated for testing the solubility of SD in PBS pH 6.8 containing 0.5%SLS as described in *section 2.2*. (All experiments were done in triplicate)

2.4.8. In-vitro drug release testing

The dissolution of an exact amount of SD equivalent to 5 mg cur was carried out over one hour in 500 mL PBS (pH 6.8) containing 0.1%SLS (USP dissolution apparatus type II (PHARMA TEST PTWS 600, Germany)). The paddle was adjusted at a speed of 100 rpm and the temperature was set at 37°C. A 5 mL aliquot was withdrawn at predetermined time intervals (10, 20 30, 40, 50, and 60 min) and replaced with an equivalent previously warmed fresh medium. Samples were filtered, and diluted and the amount of drug

was determined using UV-spectrophotometer at 421 nm. Care was taken not to withdraw insoluble particles. Release from physical mixture and SDs were investigated in comparison to pure cur.

2.5. Preparation of cur mucoadhesive tablets

Twelve tablets formulations (F_1-F_{12}), each containing an amount of solid dispersion equivalent to 10 mg cur were prepared by direct compression technique using a single punch tablet machine fitted with 8 mm round flat punches (**Table 1**).

2.6. In-vitro evaluation of cur mucoadhesive tablets

2.6.1. Physical properties of tablets

Hardness tester (Erweka TB 24) and friabilator (Roche type friabilator, Erweka TA3R) were used to test tablets hardness and friability. The thickness of 5 individual tablets was also measured using a Moore and Wright micrometer. The mean thickness and the standard deviation (S.D.) were calculated.

2.6.2. Determination of surface pH

Tablets were allowed to come in contact with 1 mL distilled water (pH 6.5±0.05) for 2 h in specially fabricated glass tubes of 15 mm diameter and 5 cm height to swell. The surface pH of the tablets was determined using a pH paper brought in contact with the swollen tablet surface. The experiment was carried out in triplicates and the mean surface pH was calculated [41].

2.6.3. In-vitro drug release testing

A locally made dissolution cell conceived in our laboratories to mimic the buccal conditions was used. The cell consisted of a 50 mL glass conical flask supplied with a rubber stopper through which passes a glass rod that ends with a 15 mm diameter round glass disc for holding the formulated tablets as previously described by Nafea et al [41] with minor modifications. **(Fig. 1)**

Fig. 1: Cells used for the in-vitro release test from tablets.

Table 1: Composition of mucoadhesive tablets formulations, (Each containing equivalent to 10 mg curcumin, 5mg Mannitol, and 1 mg Magnesium Stearate), Bioadhesion force, and in-vitro residence time.

Formula	Drug form	Ingredients mg/tablet			Weight (mg)	Bioadhesion force (dyne/cm^2)	In-vitro residence time (h)
		SLS	CMC Na	HPMC			
F_1	Cur	-	15	75	106	*	*
F_2	SD1:3	-	15	75	136	*	*
F_3	SD1:5	-	15	75	156	*	*
F_4	SD1:2	15	15	75	141	156.53±2.7	20±0.5
F_5	**SD1:3**	**15**	**15**	**75**	**151**	**154.01±2.3**	**15±1.5**
F_6	SD1:5	15	15	75	171	237.89±3.9	9.5±1
F_7	SD1:8	15	15	75	201	228.08±4.5	5±1.5
F_8	Cur	15	15	75	121	*	*
F_9	Cur	30	15	75	136	*	*
F_{10}	Cur	50	15	75	156	*	*
F_{11}	SD1:3	15	8.2	81.8	151	169.4±2.4	18± 1.25
F_{12}	SD1:3	15	25.7	64.28	151	158.8±2.1	12±2

Tablets were glued to the lower end of the glass rod using cyanoacrylate glue. The rod was then vertically placed into the conical flask filled with 20 mL of the release medium consisting of PBS (pH 6.8) containing 0.5%SLS or PEG-7-Glyceryl cocoate as a stabilizer. The level of the dissolution medium was adjusted so that the formulated tablets were just wetted but not submerged under it. The whole system was then well closed using the rubber stopper to avoid evaporation of the medium. The experiments were performed in a horizontally closed (shielded from light) shaking water bath at 100 shake/min and 37°C. The whole volume was withdrawn at previously determined time intervals (1, 2, 3, 4, 5, 6, 7, 8 h), and substituted with an equivalent volume of a previously warmed fresh medium. The amount of drug was measured spectrophotometrically at λ max 421nm [42].

2.6.4. Bioadhesive detachment test (Modified balance method)

The bioadhesive performance of the selected formulae was determined by the modified procedure of Nafee *et al*. [41] using the intestine of healthy rabbits. The force needed to detach the bioadhesive tablet from the mucosal surface was employed as a measure of the bioadhesive performance. The apparatus was locally assembled in our laboratory. It was a simple modification of the armed balance. The bioadhesion force was calculated per unit area of the tablet as follows:

F = W*g/ A

Where F is the bioadhesion force (dyne/cm^2), W is the minimum weight required to detach the tablet (g), g is the acceleration due to gravity (cm/s^2), and A is the surface area of the tablet (cm^2). The adhesion force data reported represented the mean of ten determinations [41].

2.6.5. Ex-vivo residence time determination

The USP disintegration test apparatus was modified in our laboratories for the determination of tablets residence time. The tablet was hydrated from one surface using few drops of PBS pH 6.8. The tablet was then allowed to come in contact with the rabbit intestinal mucosal membrane fixed on a glass slab, and pressed over with the fingertip for 20 sec. The glass slab was fixed vertically to the disintegration apparatus and allowed to move up and down in a way that allowed the tablet to be completely immersed in the buffer solution used. The time necessary for complete erosion of the tablet was considered as the residence time. Any signs of chipping or detachment from the mucosal surface were also recorded. The experiment was carried out in triplicates and the mean value was determined [41].

2.7. In-vivo evaluation of cur mucoadhesive tablets

From the results obtained, two selected formulations namely, (F$_4$ and F$_5$) were chosen for further in-vivo testing which were all performed after obtaining permission from the institution ethics committee of the Medical Research Institute, Alexandria University (0108096).

2.7.1. In-vivo residence time

The study was carried out on four healthy volunteers (two males and two females; age group 25-60 years). Water and food intake were not allowed half an hour before the study but were only allowed 30 min after tablet application. The volunteers were informed to press the tablets (F$_4$ and/ or F$_5$) against the buccal mucosa under the lower or the upper lip and to press onto it for (20 sec) with a dry fingertip without moistening the tablets before application. The time from tablet insertion till the end of adhesion (erosion or dislodgment of the tablets) was recorded. Volunteers were asked to report any complaints such as annoyance, unpleasant taste, dry mouth, change of salivary flow, difficulty in speaking,

inflammation, or mucosal lesions. The in-vivo residence time was defined as the interval between the applications till the time the tablet was no longer visible.

2.7.2. In-vivo release of selected tablets

Tablets formulations F_2, F_5, and F_8 were subjected to in-vivo release testing on six healthy adult human volunteers (three males and three females; age range 25- 45 years) to determine cur salivary level. No restriction on food intake, except 15 min before sampling. Volunteers were instructed not to touch the tablet with their tongues. Samples of saliva were collected before the application of the tablet and at predetermined time intervals till the complete disappearance of the tablet. One milliliter of samples of saliva were received into graduated tubes containing 10 mg SLS. This concentration of SLS (1%) is equivalent to double the concentration of SLS required to maintain cur stability for at least 24 h. Each sample was then centrifuged at 10000 rpm 4 °C for 30 min and 0.5 mL of the supernatant was then diluted with PBS pH 6.8 containing 0.5%SLS and filtered using Millipore cellulose acetate membrane filter (0.45µm). Cur concentration in each sample was detected using UV at $\lambda_{max} = 421$ nm against a salivary sample taken at zero time [43].

2.7.3. Preliminary clinical evaluation of cur mucoadhesive tablets: a case study

The preliminary clinical efficacy of cur tablets formulation F_5 was assessed on 10 volunteers age ranging between 27 to 65 years (4 males, and 6 females) suffering from aphthous ulcer. All participants gave their approval to participate in the study and informed agreement was received from all subjects involved in the study. The protocol of this study was authorized by The Institution Ethics Committee of the Medical Research Institute, Alexandria University and the work described was following the code of ethics of the World Medical Association (Declaration of Helsinki) [44]. The patients were asked to place a tablet once daily in the morning as near as possible to the affected area and to record the time required for the start of pain relief as well as any improvement in the degree of inflammation or the medical condition. Participants were asked at day zero to estimate the average pain level and for that visual analogue scale was used with a scale (0-5) where zero denoted no pain while five denoted intolerable pain. Subjects were asked to mark the pain level representing best their pain. Patients were also advised to continue the treatment until all the symptoms completely disappeared [42].

2.8. Effect of aging

The effect of aging on the drug content, dissolution rate, and bioadhesion characteristics of the selected formulation was determined after 1, 3, and 6 months, The in-vitro release and the in-vitro bioadhesion detachment tests were carried out as described earlier.

For drug assay determination, tablets were grinded in a mortar. Exactly 50 mg was transferred to a volumetric flask, cur was extracted with acetone. Samples were then filtered and appropriately diluted, and cur concentration was determined using UV spectrophotometer at λ max 421nm.

The selected formulation F_5 was stored in a clean amber well-closed glass container and was subjected to stability testing at shelf conditions (25 ±2°C and 30±5% relative humidity) for 6 months.

2.9. Statistical analysis

All results were calculated as an average of three unless otherwise stated. The in-vitro release profile and the in-vitro bioadhesion detachment strength at 0 time, after 1, 3 months, and after 6 months were compared using Wilcoxon signed ranks test. A value of $P < 0.05$ was considered statistically significant.

3. Results and Discussion

Solid dispersion is regarded as the most interesting area of research and development that relies on amorphous pharmaceutical products. SD, a mixture of a poorly water-soluble drug with hydrophilic carriers at different molecular levels, can control the drug release profile by either solubilizing or co-dissolving the drug in the soluble carriers [45].

For the selection of a suitable hydrophilic carrier for the preparation of SD, solubility of raw cur in different concentrations of HPMC, pluronic 127, and PVPK25 was conducted, where these carriers are the most well-known for SD preparation [46]. Cur showed the highest solubility in the presence of PVP K25 as shown in **Table 2.** HPMC K15 failed to increase cur solubility, while Pluronic 127 increased solubility up to 0.813 mg/mL compared to 1.167mg/mL for PVP K25. Based on the solubility results obtained, PVP was selected as a carrier for solid dispersion preparation.

Table 2: The particle size and PDI of SDs, and solubility of cur from SDs in 0.5% SLS in PBS pH 6.8 (mean ± S.D. n=3).

SD	Z-Average (nm)	PDI	Solubility (mg/mL)
SD1:1	1036 ± 343.6	0.976 ± 0.06	1.531 ± 0.053
SD1:2	202.9 ± 42.7	0.524 ± 0.12	2.877 ± 0.499
SD1:3	162.2 ± 40.3	0.644 ± 0.02	3.230 ± 0.509
SD1:5	83.90 ± 9.2	0.394 ± 0.01	8.065 ± 2.496
SD1:8	35.18 ± 2.8	0.281 ± 0.01	11.165 ± 1.732

*Solubility of cur is 0.06415 ± 0.006 mg/mL

3.1. Characterization of the prepared SDs

In this study, SDs containing PVP as a hydrophilic carrier and cur, proved to be a promising approach to improve cur dissolution profile, employing a cheap, simple, and industrially feasible technique rather than sophisticated and costly preparation methods [38, 47]. PVP being a hydrophilic carrier will increase the wettability of the SD which will be reflected in enhancing cur solubility. In addition, the melting dispersion technique requires drug solubility/miscibility, into the molten carrier which could be another limitation of some hydrophobic drugs [46].

3.1.1. FTIR

FTIR was conducted to evaluate potential interactions between cur and other components employed. **Fig. 2** showed the FTIR spectra of cur, PVP K25, physical mixture (1:2), and SD (1:2) which revealed a slight shift in the stretching vibrations of the C=O group ($1775–1650$ cm^{-1}) and the CO-C group (1597 cm^{-1}) in cur to a lower wave number. ($1190–990$ cm^{-1}) and (969 cm^{-1}) respectively. This might be due to the interaction between cur and PVP K25 and the formation of hydrogen bonding. SD 1:2 was selected as the lowest ratio that was incorporated later in tablet formulation, to avoid any masking of the peaks by excess PVP K25 that could mislead in judgment for interaction.
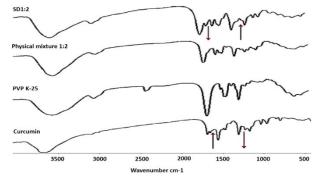

Fig. 2: FTIR spectra of cur, PVP K-25, physical mixture 1:2, and SD 1:2.

3.1.2. DSC

Based on thermal events and changes exhibited in the temperature enthalpy range, the DSC curves provide information such as melting and crystallization that can suggest physical or chemical interactions between the formulation constituents. In **Fig. 3,** the melting point of cur

is represented by the single, abrupt endothermic peak on the DSC curve of pure cur, which is found at 184.909°C and has an enthalpy of fusion of 124.010 J/g. A broad endotherm between 50 and 150 °C was seen upon PVPK25 scanning, which indicates water loss as a result of the polymer glass transition temperature and the highly hygroscopic character of PVP polymers. Given that water acts as a plasticizer and lowers Tg, the reduced PVP glass transition temperature (Tg) indicates that the polymer has absorbed water, which was previously explained by Frizon et al [48].

For the physical mixture, a wide endotherm with a peak temperature shifted to a lower temperature (181.597°C) than pure cur was observed in the DSC curves. Due to PVP K25's solubilizing impact throughout the heating process, cur's enthalpy of fusion also dropped (17.079 J/g); only excess cur exhibited a melting endotherm, indicating the presence of cur in its crystalline state. Otherwise, SDs didn't display any endothermic cur peaks. When the thermal characteristics of cur vanish, SD system is disseminated in its amorphous form. When PVP is utilized in SDs as a carrier, this behavior frequently occurs.
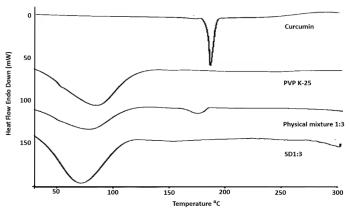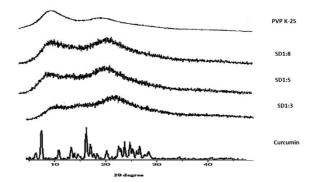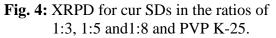

Fig. 3: DSC thermograms of cur, PVP K-25, SD1:3, and physical mixture1:3.

3.1.3. XRPD
Based on the diffractograms (**Fig. 4**), pure cur exhibited many well-defined peaks at 2θ due

to its crystalline nature. Otherwise, XRPD patterns of SDs manifested distinct broad peaks. This broadening of the peak indicated the formation of an amorphous form that confirmed the ability of the PVP matrix to suppress cur crystallization. These results were in accordance with findings reported by Paradkar *et al.* [38] and Kaewnopparat *et al.* [35].

Fig. 4: XRPD for cur SDs in the ratios of 1:3, 1:5 and1:8 and PVP K-25.

3.1.4. Particle size and polydispersity index (PDI) analysis
It's also worth mentioning that a significant decrease in particle size was observed with increasing PVP K25 concentration. It was suggested that the more PVP K25 added, the higher the conversion of the drug from the crystalline to the highly disordered amorphous form. Similarly, a significant decrease in the PDI was observed as the concentration of PVP K25 increased, indicating that a more homogenous sample was achieved (**Table 2**).

Table 2: The particle size and PDI of SDs, and solubility of cur from SDs in 0.5% SLS in PBS pH 6.8 (mean ± S.D. n=3).

SD	Z-Average (nm)	PDI	Solubility (mg/mL)
SD1:1	1036 ± 343.6	0.976 ± 0.06	1.531±0.053
SD1:2	202.9 ± 42.7	0.524 ±0.12	2.877±0.499
SD1:3	162.2 ± 40.3	0.644 ±0.02	3.230±0.509
SD1:5	83.90 ± 9.2	0.394 ±0.01	8.065±2.496
SD1:8	35.18 ± 2.8	0.281 ±0.01	11.165±1.732

*Solubility of cur is 0.06415±0.006 mg/mL

108

3.1.5. SEM

The micrographs confirmed the irregular size and morphology of cur crystals (**Fig. 5**). The SEM micrographs of cur SD (1:3), showed less organized particles which indicate the incorporation of the cur into the PVPK25, confirming results obtained by XRPD. SD (1:3) was selected for this test, as it is the one used in the optimized tablet formulation chosen for further clinical investigation *(section 3.7).*
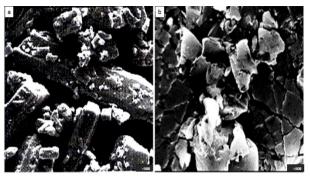

Fig. 5: SEM photos of (a) pure cur and (b) cur SD1:3.

3.2. Chemical stability studies and stabilizers screening

Cur, diferuloylmethane, is 2-hydroxy methoxyphenolic rings connected by 2 β-diketone groups. This structure is unstable under physiological conditions where it decomposed to inactiveTrans-6-(40-hydroxy-30-methoxyphenyl)-2, ferulic acid, 4-dioxo-5-hexanal, vanillin, and feruloylmethane [49-51] This finding necessitates the investigation of cur chemical stability in the prepared formulations to decide the need for incorporation of stabilizer or not. For this purpose, PBS pH 6.8 at 37°C was chosen as a medium for testing cur chemical stability to mimic the intra-oral physiological conditions at which the pH ranges from 5.5-7 [52].

Both cur and SD (1:8) were found to be susceptible to degradation under these conditions and they both showed similar degradation profiles where about 38%, 45%,

and 50% of cur was degraded in PBS pH 6.8 at 37°C within 1h, 2h, and 3h, respectively proving that PVP K25 failed to stabilize cur and the need for using a stabilizer

As a screening step, polymers and a variety of SAA were tested for their ability to stabilize cur. PVP K25 and HPMC K15M failed to maintain the drug stability even at very high concentrations. On the other hand, all tested SAAs were found to be effective in maintaining the stability of cur. Different concentrations of SLS and PEG-7-glyceryl cocoate in PBS pH6.8 (2%, 1%, and 0.5%) showed a significant ($p<0.5$) improvement in cur stability over 24h compared to cur in PBS pH 6.8 (**Fig. 6&7**). The improvement of cur or SD stability could be attributed to the entrapment of cur within SAA micelles protecting it against degradation [53].
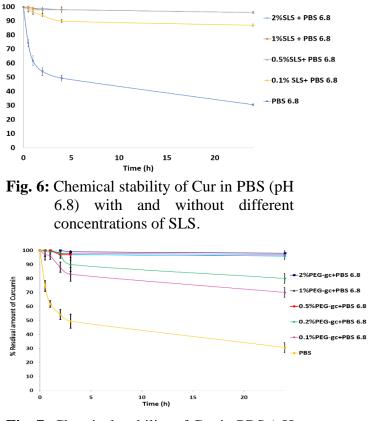

Fig. 6: Chemical stability of Cur in PBS (pH 6.8) with and without different concentrations of SLS.

Fig. 7: Chemical stability of Cur in PBS (pH 6.8) with and without different concentrations of PEG.gc.

3.3. Solubility studies

The solubility of cur and different SDs in varied PVP K25 concentrations was carried out. For all SDs, cur solubility was markedly improved over that of pure cur. SDs 1:1, 1:2, 1:3, 1:5, and 1:8 showed 24, 45, 50, 126, and 174-fold increases in solubility compared to pure cur, respectively. Results declared the increased cur solubility with increasing PVP K25 amount. The test was carried out in the presence of SLS to maintain stability over the study period. It is worth noting that to exclude the solubilization effect of SLS, the solubility of raw cur powder was carried out at the same conditions as a reference for comparison. Data are depicted in **Table 3.**

Table 3: solubility of Curcumin in PBS pH 6.8 containing 0.5 % SLS and different ratios of polymers (mean±S.D. n=3).

Polymer	w/v %	Solubility (mg/ml)
-	-	0.0641 ± 0.006
HPMC K15	0.2%	0.066 ± 0.004
	0.5%	0.069 ± 0.002
	1.0%	0.065 ± 0.006
P127	2%	0.332 ± 0.005
	4%	0.381 ± 0.003
	6%	0.563 ± 0.061
	8%	0.813 ± 0.002
PVP K-25	2%	0.886 ± 0.100
	4%	1.068 ± 0.250
	6%	1.243 ± 0.065
	8%	1.617 ± 0.045

3.4. In-vitro drug release testing

PBS (pH 6.8) was selected as a medium for solubility and dissolution studies testing to simulate the oral cavity condition, SLS was added to the medium only for stabilization purposes. This test uniquely describes dissolution using a dissolution medium mimicking the physiological pH taking into consideration the drug stability. On the contrary, Paradkar and colleagues used 0.1N HCl as dissolution media which is different from actual physiological condition [38].

However, in our work, SLS was selected as it is commonly reported to be used in dissolution media for creating sink conditions without any precautions.

The selection of 0.1%SLS was based on the minimum concentration of SLS that could maintain cur stability during the experimental period with minimum solubilization effect.

Fig. 8 shows that the higher the amount of PVP K25 in the solid dispersion the higher the release rate. Thus, SD1:8 showed the highest release rate. In addition, release from SD1:8, SD1:5, and SD1:3 reached 100% after 10 min, 20 min, and 30 min, respectively. This was attributed to increased solubility of the prepared formulation where SD allowed cur to co-precipitate with PVP 25 in an amorphous form as well as improved drug wettability as a result of PVP K25 incorporation.
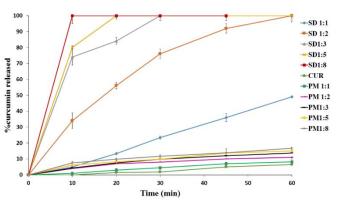

Fig. 8: Dissolution profiles of cur, physical mixtures, and SDs in 0.1%SLS+PBS pH 6.8.

3.5. In-vitro evaluation of cur mucoadhesive tablets

3.5.1. Thickness, hardness and friability

Tablets thickness ranged from 1.51 to 2.52 mm, which was quite suitable for oral cavity application causing no discomfort to the patient or dislodgement. The mechanical strength of all tablets ranged from 4-4.5 kg/cm² and friability was less than 1% i.e. the

tablets were not fragile or brittle and could be easily handled without being broken.

3.5. 2. Surface pH

All tablets formulations provided an acceptable surface pH ranging from 6.5 to 7.5 close to neutral pH thus not irritating the oral mucosa.

3.6. In-vitro drug release testing

The release rate study in PBS pH 6.8 as a release medium containing no stabilizer failed to show any significant amount of cur released from different tablets formulations containing either cur in its pure form (F_1) or in the form of solid dispersion SD1:3 (F_2), or SD1:5 (F_3), as shown in **Fig. 9a**. This could be attributed to the hydrolytic degradation of cur released from the formulation assuring the need of including an appropriate stabilizer in the release medium to avoid cur degradation during in-vitro release testing.

For this purpose, 0.5% PEG-7-Glyceryl cocoate /or 0.5% SLS in PBS pH 6.8 were studied for their efficacy in acting as a stabilizer for the released cur. Using SLS stabilized media showed a higher release rate than that in the case of using PEG-7-Glyceryl cocoate where 64% and 40.5% of Cur was released from F_2 in 24 h respectively **(Fig. 9b).**

To confirm that the amount released did not undergo degradation, the amount of cur remaining in tested tablets after completing the dissolution testing was examined. After the end of the experiment the tested tablets were collected, and cur was extracted using acetone. Samples were filtered, properly diluted, and analyzed using UV spectrophotometer. The amounts of cur recovered were 36% and 30% for media containing SLS and PEG-7-Glyceryl cocoate as a stabilizer, respectively. This confirmed that the use of a stabilizer helped maintain cur stability. Using SLS showed better cur recovery where the total amount of cur in the tablet was fully recovered, compared to only

70.5% recovered in case of using PEG-7-Glyceryl cocoate.

From this finding, it is clear that the presence of SLS is a must to ensure cur stability in the dissolution medium, a condition that is not satisfied in the saliva, therefore 15mg SLS was incorporated in each tablet formulation to be released in concomitant to cur released from the tablet upon application to the buccal mucosa. The selection of SLS was based on being efficient in cur stabilization, in addition to its solid nature making it easily incorporated in tablet mixture compared to the liquid nature of PEG-7-glyceryl cocoate. 15 mg SLS / tablet was chosen after testing drug release in the presence of different concentrations of SLS (15, 30, and 50 mg) in comparison to the 0 SLS /tablet. Results showed that all 3 concentrations showed the same stabilizing power and therefore minimum concentration (15 mg) was chosen. **(Fig. 9c).**

Formulations F_4, F_5, F_6, F_7, and F_8 containing SLS showed sustained release profiles with a total amount of 38%, 29.1%, 26.4%, 33.9%, and 15.3% released after 8 h, respectively. However, after 10 h fragmentation of F_7 was recorded which was accompanied by a sudden increase in the release rate as shown in **Fig. 9d**.

The release mechanism from the tablet formulations F_4, F_5, F_6, F_7, and F_8 was complicated, where different variables contributed such as drug particle size, drug solubility, PVP concentration, total tablet weight, tablet thickness, and drug/polymer ratio.

During the initial stages of hydration, the release was mainly governed by the HPMC and CMC Na content. As the release proceeds, PVP starts to diffuse throughout the tablet matrix into the diffusion layer resulting in increasing the viscosity thus retarding drug release. Afterward, PVP dissolved leading to channel formation, and consequently, increased drug release rates. In

111

case of formulation containing higher PVP concentration such as F_7 containing SD1:8, higher porosity and channels formed through the matrix, resulted in matrix destruction.

F_8 containing pure cur showed 32.4% cumulative drug released over 24 h which may be attributed to the in situ solubilizing effect of SLS incorporated into the tablet matrix. Moreover, the impact of various SLS concentrations on the pure cur's release profile was examined. No variation in the drug release profiles was noted, which is consistent with findings reported by Nokhodchi et al.[54] examining the impact of

utilizing varying SLS concentrations with captopril.

Tablets formulations F_{11}, F_5, and F_{12} containing different CMC Na: HPMC ratios showed 19.4%, 22.5%, and 26% of drug released at 6 h with cumulative drug release 51.3%, 70%, and 75.2% at 24 h. This indicates that increasing CMC Na content results in a higher release rate probably due to CMC sodium's greater hydration and dissolving qualities. CMC sodium forms a colloidal dispersion in the HPMC matrix resulting in a more porous structure thus increasing erosion and release rate
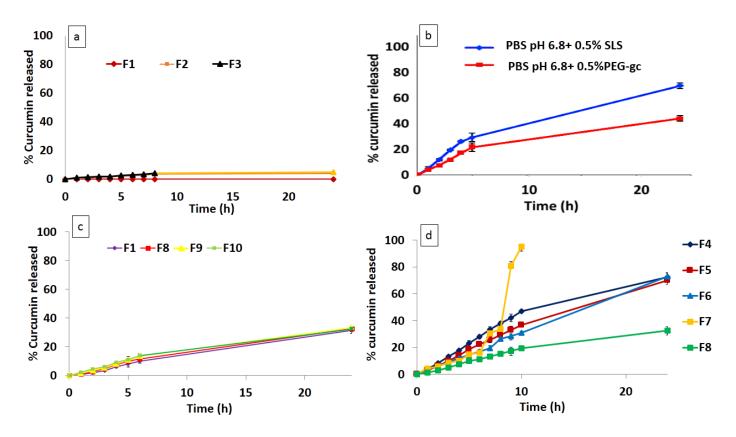

Fig. 9: Drug release profiles from non-stabilized tablets F_1 (pure cur), F_2 (SD1:3), and F_3 (SD1:5) in PBS pH 6.8 **(a)**. Drug release profiles from non-stabilized tablet F_2 (SD1:3) in two stabilized release media 0.5%PEG-7-Glycerylcocoate in PBS or 0.5% SLS in PBS pH 6.8 **(b)**. Drug release profiles from tablets F_1, F_8, F_9, and F_{10} containing pure cur with 0mg, 15mg, 30mg, and 50mg SLS, respectively **(c)**. Drug release profiles from stabilized tablets containing 15mg SLS; F8 containing pure cur, F_4 (SD1:2), F_5 (SD1:3), F_6 (SD1:5), and F_7 (SD1:8) in 0.5 %SLS in PBS pH 6.8 **(d)**.

3.6.1. In-vitro bioadhesion and residence time studies

The majority of experimental animals, in contrast to humans, have completely keratinized mouth linings. The mucosal lining of laboratory rats resembles human tissue but isn't keratinized, mucosal linings that are not keratinized are only seen in rabbits. However, the abrupt shift to keratinized tissue at the mucosal borders, makes it challenging to isolate the necessary non-keratinized portion. Due to the high expenses of getting pigs, another alternative was considered. The rabbit intestine was selected as a mucosal membrane only for discrimination of the prepared formulations especially since the drug should act locally and the formulation is not aiming to test permeation. In addition, it has been previously reported by Nafea and co-author that using rabbit intestine was successful in the discrimination of different mucoadhesive buccal patches [55]. The bioadhesion detachment strengths and in-vitro residence time were carried out for promising formulations: F_4, F_5, F_6, F_{11}, and F_{12}. Tested tablets showed comparatively similar values for the bioadhesion detachment strength ranging from 154.01 dyne/cm^2 to 237.89 dyne/cm^2, which might be attributed to the same or narrow range of polymers ratio used in all formulations. However, F_6 and F_7 showed slightly higher bioadhesion strength which could be due to the higher concentration of the mucoadhesive polymer PVP incorporated in those formulations. In-vitro residence time ranged from 5 h to 20 h which was a main advantage for tablets over buccal films or gels as it can provide longer residence time, thus longer duration of action. From the results obtained, F_4 and F_5 were selected for further investigation where they showed the highest in-vitro residence time 20 h and 15 h, respectively (**Table** 1).

3.7. In-vivo evaluation

The selected tablets F_4 and F_5 were found to have an in-vivo residence duration of 17 ± 1.5 h for F_4 (containing SD1:2) and 12 ± 1 h for F_5 (containing SD1:3) after which the tablets were completely solubilized leaving no fragment with no need to be removed by the patient. Based on the results obtained, tablet formula F_5 was selected as it showed optimum release behavior and in-vivo residence time.

Formula F5 was evaluated in vivo on healthy volunteers, and the results showed that the tablets dissolved without causing any discomfort after around 12 h. The taste was satisfactory, and there were no adverse effects such as changes in taste, or excessive salivation. Salivary cur concentrations over 12 h study period ranged between 18.58 ± 7.3 and 76.5 ± 19.8 μg/mL, **Fig. 10 a**. These findings declared the potential of improved solubility and stability of cur in F_5 that could successfully maintain cur levels in saliva over 12 h.

3.7.1. Preliminary clinical evaluation

The preliminary clinical efficacy of cur tablets was evaluated to ensure the efficacy of the delivery system adopted to stabilize cur and maintain its efficacy. The formula F_5 was assessed on patients suffering from recurrent aphthous ulcers associated with pain and inflammation. The beginning of pain relief started from 30 min to 1 h in all cases. The curing time for all patients ranged from 1-3 days. These results may indicate that the F_5 tablet can be considered suitable for clinical use on a once or twice-daily regimen. The relief of pain was attributed to the anti-inflammatory properties of cur, which reduced inflammation thus decreasing pain sensation. Hazzah *et al.* [42] obtained similar outcomes using cur solid lipid nanoparticles incorporated into mucoadhesive gel where reduced pain and rapid healing of precancerous oral lesions were observed. The complete healing was achieved after six

weeks of treatment which could be attributed to the lower residence time of gel compared to tablets in this current study [42], **Fig. 10 b.**
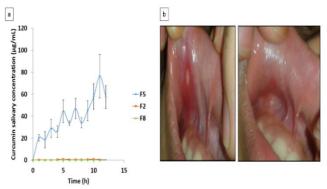

Fig.10: Salivary drug concentrations after a single application of F_2 (SD 1:3, 15 mg SLS), F_5 (SD 1:3, 0 mg SLS) and F_8 (pure cur, 15 mg SLS) over 12 h on six healthy adult human volunteers (three males and three females; age range 25- 45 years) (a), A 31 years old woman suffers from aphthous ulcer in the inner wall of upper lip, (left) before treatment and (right) after application of one tablet F_5 (b).

3.8. Effect of aging

The effect of aging was conducted on formulation F_5, regarding drug content, bioadhesion, and release rate. No significant difference ($p > 0.5$) was found in all test parameters during the storage period of 3 and 6 months, respectively.

4. Conclusions

Modern-day therapy used in the management of inflammatory oral conditions suffers from many disadvantages such as reduced contact time, numerous side effects, and limited efficacy. Therefore, the incorporation of a natural active ingredient such as cur with proven excellent anti-inflammatory, antibacterial, and analgesic properties in mucoadhesive tablet seemed a valuable approach. However, it has been ignored for buccal application as it suffered from many problems such as chemical instability and insolubility in the oral environment. Interestingly, results described in this work overcome these obstacles using cur solid dispersion with PVP K25 as a simple solution to the solubility problem at low expenses. A low concentration of SLS was required for maintaining cur stability. Cur stabilized mucoadhesive tablet was successful and showed outstanding management of oral inflammatory conditions. Mucoadhesive tablets increased the contact time and consequently duration of action at the inflammation site resulting in rapid pain relief and healing as proven by preliminary clinical studies. However, a further detailed clinical study is recommended in future work to adjust the dose and dosing regimen and to specify the condition of use on larger human samples and in the presence of control.

Authors' contributions

All authors contributed equally to this work.
Ossama Y. Abdallah came up with the original concept for the article. He also designed the analysis, helped with research design, assisted with data interpretation, oversaw the writing process, and reviewed the manuscript.
Heba MK Ebada conducted the literature search, carried out the experiments, gathered and analyzed the data, and authored the first draft.
Maha MA Nasra made contributions to the supervision, data interpretation, study design, and manuscript revision.
Heba A. Hazzah made contributions to the writing, editing, and publication of the work as well as the analysis of the experimental data and results.

Institutional review board

The Medical Research Institute's (0108096) Ethics Committee gave its approval to the study, which was carried out in accordance with the Declaration of Helsinki's principles.

Data availability

The corresponding author can provide the data from this study upon request.

Conflict of interest

As stated by the authors, there is none.

Highlights

- Amorphous cur solid dispersion improved cur solubility problem at low expenses.
- SLS exhibited excellent cur stability in in-vitro and in-vivo studies.
- Mucoadhesive tablets increased the contact time resulting in rapid pain relief.
- Cur stabilized mucoadhesive tablet showed a promising healing effect.

Abbreviations

cur; curcumin, SD; solid dispersion

Declaration of interests

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

5. References

(1) Mitra S, Tareq AM, Das R, Emran TB, Nainu F, Chakraborty AJ, *et al.* Polyphenols: A first evidence in the synergism and bioactivities. Food Reviews International. 2023;39(7):4419-41.

(2) Obeid MA, Alsaadi M, Aljabali AA. Recent updates in curcumin delivery. Journal of liposome research. 2023;33(1):53-64.

(3) Abolfazli S, Butler AE, Jamialahmadi T, Sahebkar A. A Golden Shield: The Protective Role of Curcumin Against Liver Fibrosis. Current Medicinal Chemistry. 2024.

(4) Murtadlo AAA, Ansori ANM, Dhea V, Turista DR, Rosadi I, Jakhmola V, *et al.* A Mini Review of Curcuma longa: Antimicrobial Properties. 2024.

(5) Das D, Mitra A, Zaky MY, Pathak S, Banerjee A. A Review on the Efficacy of Plant-derived Bio-active Compounds Curcumin and Aged Garlic Extract in Modulating Cancer and Age-related Diseases. Current Reviews in Clinical and Experimental Pharmacology Formerly Current Clinical Pharmacology. 2024;19(2):146-62.

(6) Dunsmore KE, Chen PG, Wong HR. Curcumin, a medicinal herbal compound capable of inducing the heat shock response. Critical care medicine. 2001;29(11):2199-204.

(7) Kuhad A, Pilkhwal S, Sharma S, Tirkey N, Chopra K. Effect of curcumin on inflammation and oxidative stress in cisplatin-induced experimental nephrotoxicity. Journal of agricultural and food chemistry. 2007;55(25):10150-5.

(8) Ohori H, Yamakoshi H, Tomizawa M, Shibuya M, Kakudo Y, Takahashi A, *et al.* Synthesis and biological analysis of new curcumin analogues

bearing an enhanced potential for the medicinal treatment of cancer. Molecular cancer therapeutics. 2006;5(10):2563-71.

(9) Mehta P, Bhavasar R, Ajith NA, Bhavsar RP, Bahammam MA, Bakri MMH, *et al.,* editors. Assessing the effect of curcumin on the oral mucosal cytomorphometry and candidal species specificity in tobacco users: a pilot study. Healthcare; 2022: MDPI.

(10) Hajifathali S, Lesan S, Lotfali E, Salimi-Sabour E, Khatibi M. Investigation of the antifungal effects of curcumin against nystatin-resistant Candida albicans. Dental Research Journal. 2023;20.

(11) Chen CW, Hsieh MJ, Ju PC, Hsieh YH, Su CW, Chen YL, *et al.* Curcumin analog HO-3867 triggers apoptotic pathways through activating JNK1/2 signalling in human oral squamous cell carcinoma cells. Journal of Cellular and Molecular Medicine. 2022;26(8):2273-84.

(12) Al-Askar M, AlMubarak AM, Alqutub MN, Mokeem S, Javed F, Vohra F, *et al.* Analgesic Efficacy of Curcuma longa (Curcumin) after Surgical Periodontal Therapy. Oral Health Prev Dent. 2022;20:19-26.

(13) Sterniczuk B, Rossouw PE, Michelogiannakis D, Javed F. Effectiveness of Curcumin in Reducing Self-Rated Pain-Levels in the Orofacial Region: A Systematic Review of Randomized-Controlled Trials. International Journal of Environmental Research and Public Health. 2022;19(11):6443.

(14) Huang X, Liu Y, Wang Q, Rehman HM, Horváth D, Zhou S, *et al.* Brief literature review and comprehensive bioinformatics analytics unravel the potential mechanism of curcumin in the treatment of periodontitis. BMC Oral Health. 2023;23(1):469.

(15) Nair VV, Cabrera P, Ramírez-Lecaros C, Jara MO, Brayden DJ, Morales JO. Buccal delivery of small molecules and biologics: of mucoadhesive polymers, films, and nanoparticles–An update. International Journal of Pharmaceutics. 2023:122789.

(16) Jana BK, Singh M, Dutta RS, Mazumder B. Current drug delivery strategies for buccal cavity ailments using mouth dissolving wafer technology: a comprehensive review on the present state of the art. Current Drug Delivery. 2024;21(3):339-59.

(17) Dattatray JA, Nalawade DD, Prasad KC. A review on mucoadhesive buccal drug delivery. Research Journal of Science and Technology. 2023;15(3):153-60.

(18) Khater A-J, Almurisi SH, Mahmood S, Madheswaran T, Chatterjee B, Sri P, *et al.*

115

Strategies to improve the stability of amorphous solid dispersions in view of the hot melt extrusion (HME) method. International Journal of Pharmaceutics. 2023:123536.

(19) Budiman A, Handini AL, Muslimah MN, Nurani NV, Laelasari E, Kurniawansyah IS, *et al.* Amorphous Solid Dispersion as Drug Delivery Vehicles in Cancer. Polymers. 2023;15(16):3380.

(20) Li J, Wang Y, Yu D. Effects of Additives on the Physical Stability and Dissolution of Polymeric Amorphous Solid Dispersions: a Review. AAPS PharmSciTech. 2023;24(7):175.

(21) Valenti S, Arioli M, Jamett A, Tamarit JL, Puiggalí J, Macovez R. Amorphous solid dispersions of curcumin in a poly (ester amide): Antiplasticizing effect on the glass transition and macromolecular relaxation dynamics, and controlled release. International journal of pharmaceutics. 2023;644:123333.

(22) Xi Z, Fei Y, Wang Y, Lin Q, Ke Q, Feng G, *et al.* Solubility improvement of curcumin by crystallization inhibition from polymeric surfactants in amorphous solid dispersions. Journal of Drug Delivery Science and Technology. 2023;83:104351.

(23) Siripruekpong W, Issarachot O, Kaewkroek K, Wiwattanapatapee R. Development of Gastroretentive Carriers for Curcumin-Loaded Solid Dispersion Based on Expandable Starch/Chitosan Films. Molecules. 2023;28(1):361.

(24) Han J, Wei Y, Li L, Song Y, Pang Z, Qian S, *et al*. Gelation elimination and crystallization inhibition by co-amorphous strategy for amorphous curcumin. Journal of Pharmaceutical Sciences. 2023;112(1):182-94.

(25) Feng Y, Li B, Yang L, Liu Y. Co-amorphous delivery systems based on curcumin and hydroxycinnamic acids: Stabilization, solubilization, and controlled release. LWT. 2022;170:114091.

(26) Maleki Dizaj S, Sharifi S, Tavakoli F, Hussain Y, Forouhandeh H, Hosseiniyan Khatibi SM, *et al*. Curcumin-Loaded silica nanoparticles: Applications in infectious disease and food industry. Nanomaterials. 2022;12(16):2848.

(27) Tran T-T, Chua A, Pu S, Park J-W, Hadinoto K. Maintaining supersaturation generation and protein integrity of amorphous curcumin-albumin nanoplex during storage by freeze drying with trehalose. Journal of Drug Delivery Science and Technology. 2023;83:104425.

(28) Teixeira C, Mendonca L, Bergamaschi M, Queiroz R, Souza G, Antunes L, *et al.* Microparticles containing curcumin solid dispersion: stability, bioavailability and anti-inflammatory activity. AAPS PharmSciTech. 2016;17(2):252-61.

(29) Chuah AM, Jacob B, Jie Z, Ramesh S, Mandal S, Puthan JK, *et al*. Enhanced bioavailability and bioefficacy of an amorphous solid dispersion of curcumin. Food chemistry. 2014;156:227-33.

(30) Song I-S, Cha J-S, Choi M-K. Characterization, in vivo and in vitro evaluation of solid dispersion of curcumin containing d-α-Tocopheryl polyethylene glycol 1000 succinate and mannitol. Molecules. 2016;21(10):1386.

(31) Li J, Lee IW, Shin GH, Chen X, Park HJ. Curcumin-Eudragit® E PO solid dispersion: a simple and potent method to solve the problems of curcumin. European Journal of Pharmaceutics and Biopharmaceutics. 2015;94:322-32.

(32) Wan S, Sun Y, Qi X, Tan F. Improved bioavailability of poorly water-soluble drug curcumin in cellulose acetate solid dispersion. AAPS PharmSciTech. 2012;13(1):159-66.

(33) Parikh A, Kathawala K, Song Y, Zhou X-F, Garg S. Curcumin-loaded self-nanomicellizing solid dispersion system: part I: development, optimization, characterization, and oral bioavailability. Drug delivery and translational research. 2018:1-17.

(34) Zhang Q, Suntsova L, Chistyachenko YS, Evseenko V, Khvostov MV, Polyakov NE, *et al*. Preparation, physicochemical and pharmacological study of curcumin solid dispersion with an arabinogalactan complexation agent. International journal of biological macromolecules. 2019;128:158-66.

(35) Kaewnopparat N, Kaewnopparat S, Jangwang A, Maneenaun D, Chuchome T, Panichayupakaranant P. Increased solubility, dissolution and physicochemical studies of curcumin-polyvinylpyrrolidone K-30 solid dispersions. World academy of science, engineering and technology. 2009;55:229-34.

(36) Alves TF, Chaud MV, Grotto D, Jozala AF, Pandit R, Rai M, *et al*. Association of silver nanoparticles and curcumin solid dispersion: antimicrobial and antioxidant properties. AAPS PharmSciTech. 2018;19(1):225-31.

(37) Hernandez-Patlan D, Solis-Cruz B, Pontin KP, Latorre JD, Baxter MFA, Hernandez-Velasco X, *et al*. Evaluation of a Solid Dispersion of Curcumin With Polyvinylpyrrolidone and Boric Acid Against Salmonella Enteritidis Infection and Intestinal Permeability in Broiler Chickens: A Pilot Study. Frontiers in microbiology. 2018;9:1289.

(38) Paradkar A, Ambike AA, Jadhav BK, Mahadik KR. Characterization of curcumin–PVP solid dispersion obtained by spray drying. International Journal of Pharmaceutics. 2004;271(1):281-6.

(39) Hazzah HA, Farid RM, Nasra MM, Hazzah WA, El-Massik MA, Abdallah OY. Gelucire-based nanoparticles for curcumin targeting to oral mucosa: preparation, characterization, and antimicrobial activity assessment. Journal of pharmaceutical sciences. 2015;104(11):3913-24.

(40) El-Refaie WM, Elnaggar YS, El-Massik MA, Abdallah OY. Novel curcumin-loaded gel-core hyaluosomes with promising burn-wound healing potential: development, in-vitro appraisal and in-vivo studies. International journal of pharmaceutics. 2015;486(1-2):88-98.

(41) Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive delivery systems. I. Evaluation of mucoadhesive polymers for buccal tablet formulation. Drug development and industrial pharmacy. 2004;30(9):985-93.

(42) Hazzah HA, Farid RM, Nasra MM, Zakaria M, Gawish Y, El-Massik MA, *et al.* A new approach for treatment of precancerous lesions with curcumin solid–lipid nanoparticle-loaded gels: in vitro and clinical evaluation. Drug delivery. 2016;23(4):1409-19.

(43) Hazzah HA, Farid RM, Nasra MM, EL-Massik MA, Abdallah OY. Lyophilized sponges loaded with curcumin solid lipid nanoparticles for buccal delivery: Development and characterization. International journal of pharmaceutics. 2015;492(1-2):248-57.

(44) Association WM. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization. 2001;79(4):373.

(45) Vasconcelos T, Marques S, das Neves J, Sarmento B. Amorphous solid dispersions: rational selection of a manufacturing process. Advanced drug delivery reviews. 2016;100:85-101.

(46) Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN pharmaceutics. 2012;2012.

(47) Xu D-H, Wang S, Jin J, Mei X-T, Xu S-B. Dissolution and absorption researches of curcumin in solid dispersions with the polymers PVP. Asian J Pharmacodyn Pharmacokinet. 2006;6(4):343-9.

(48) Frizon F, de Oliveira Eloy J, Donaduzzi CM, Mitsui ML, Marchetti JM. Dissolution rate enhancement of loratadine in polyvinylpyrrolidone K-30 solid dispersions by solvent methods. Powder technology. 2013;235:532-9.

(49) Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. Biochemical pharmacology. 2008;75(4):787-809.

(50) Lee BH, Choi HA, Kim M-R, Hong J. Changes in chemical stability and bioactivities of curcumin by ultraviolet radiation. Food Science and Biotechnology. 2013;22(1):279-82.

(51) Seo S-W, Han H-K, Chun M-K, Choi H-K. Preparation and pharmacokinetic evaluation of curcumin solid dispersion using Solutol® HS15 as a carrier. International journal of pharmaceutics. 2012;424(1-2):18-25.

(52) Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. Journal of controlled release. 2011;153(2):106-16.

(53) Wang Z, Leung MH, Kee TW, English DS. The role of charge in the surfactant-assisted stabilization of the natural product curcumin. Langmuir. 2009;26(8):5520-6.

(54) Nokhodchi A, Hassan-Zadeh D, Monajjem-Zadeh F, Taghi-Zadeh N. Effect of various surfactants and their concentration on controlled release of captopril from polymeric matrices. Acta Pharmaceutica. 2008;58(2):151-62.

(55) Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. International journal of pharmaceutics. 2003;264(1-2):1-14.