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Co-Milling: A Successful Approach to Enhance Solubility of a Poorly Soluble Antihypertensive Drug

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ABSTRACT

The aim of the work was to enhance the solubilization of olmesartan-medoxomil (OM) and formulate stable, fast-dissolving-tablets (FDTs) formulations. However, OM is classified as a Biopharmaceutics Classification System (BCS) Class II drug, which indicates that it is characterised by poor solubility. Therefore, boosting its solubilization has the potential to boost its bioavailability. For the OM evaluation, a new HPLC technique was developed and then validated in accordance with international standards such as International Conference Harmonisation (ICH) and Food and Drug Administration (FDA) guidance. Twelve FDT-formulations were prepared using co-milling with superdisintegrants such as croscarmellose sodium (Ac-Di-Sol) and Crospovidone type A in varied percentages, followed by mixing with pH-adjusting substances such as calcium carbonate to increase solubilization in cases where the drug is soluble in alkaline. Following the evaluation of the created formulations, the optimised formulations were selected for further stability assessment. Co-milling process with Crospovidone greatly improved the OM release. The optimised formulations were OD11 and OD12, which exhibited fast disintegration, and the release exceeded 90% within 10 min, while the release for OM pure standard was 9.8% after 10 min. The OD11 and OD12 were chosen for further stability assessment and revealed good stability behaviour, as the study on optimised formulations revealed that the degradation was less than 5% after storage for six months at 40 °C and 75% relative humidity. Some formulations exhibited good results in terms of disintegration and release. To sum up, co-grinding with Crospovidone could increase the solubilization of OM.

Keywords: Ac-Di-Sol, BCS II, Co-milling, Crospovidone, HPLC, Olmesartan medoxomil.

INTRODUCTION

Hypertension is considered the "secret killer" as it does not show its initial symptoms, which are the most dangerous reasons for heart disease such as enlarged heart muscle, congestive heart failure, stroke, and chronic kidney disease. Complications of high blood pressure are correlated with either persistent increases, changes in the heart, or atherosclerosis associated with long-term hypertension (Vaughan *et al*., 2022). Therefore, the treatment of hypertension is crucial for protecting against many other associated diseases. An angiotensin II receptor antagonist, Olmesartan medoxomil, or OM, is responsible for the reduction of blood pressure. It is taken once a day in a dose that ranges from 20 mg to 40 mg (Alan *et al*., 2020). The time period between one and three hours is when the plasma concentration of OM is at its highest. Oral bioavailability of OM is between 26% and 28.6% (González *et al*., 2022; Koike *et al*., 2003), according to research done by both groups. OM does not dissolve in water, but it does dissolve more easily in acidic and basic solutions, and it has a pH-lowering effect (4.0–6.0). (Arun *et al*., 2018; Al-Shdefat *et al*., 2020).

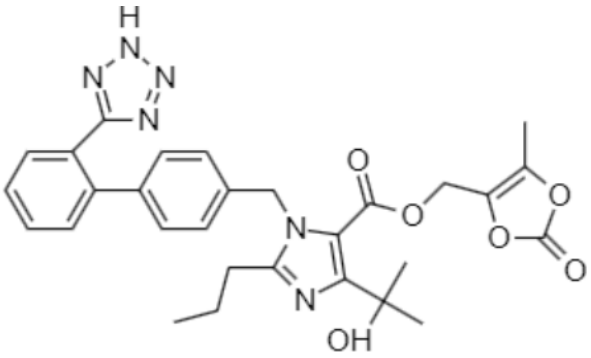

Figure 1. Chemical structure of OM

A drug with low solubility was more difficult to incorporate into oral dosage forms. For a dosage form to achieve optimal bioavailability, enhancing solubility is the primary concern. FDTs Fast-dissolving tablets (FDTs) are beneficial for patients who have difficulty swallowing conventional tablets, such as paediatric patients, patients undergoing chemotherapy treatment, and mentally ill patients, because they permit rapid dissolution of dosage forms in the mouth. (Eisa *et al*., 2022). The low water solubility and high membrane permeability of some drugs necessitate the use of methods such as chemical modification, changing the composition of the solvent, using a carrier system, physical modification, and cogrinding. These are just some of the methods that are used to reduce the poor solubility of some drugs, particularly those that are classified as BCS Class II drugs (Martindle, 2011; USP, 2019; Choursiya & Pandit, 2021). The rate of absorption will increase in tandem with the rate of dissolution. As a result, using of crospovidone and Ac-Di-Sol as superdisintegrants was performed to achieve rapid disintegration and permit quick drug dissolving (Husseiny *et al*., 2018). The aim of our investigation is to improve the solubilization of OM, as it belongs to BCS Class II, using co-milling with previous superdisintegrants such as croscarmellose and crospovidone type A with a morter and pestle for 2 h, then the addition of calcium carbonate to render the drug's medium in a highly alkaline environment to increase its dissolution. Twelve FDTs formulations were formulated and assessed concerning weight variation, uniformity, friability, time to disintegrate, time of wetting, dispersion, and release.

MATERIALS AND METHODS

Olmesartan medoxomil (99.6%, HPLC) was purchased from Ami Lifesciences. Calcium carbonate, lactose fast flow, Ac-Di-Sol, crospovidone type A, and magnesium stearate are provided by Wadi Elrafideen for pharmaceuticals, Iraq. Acetonitrile, triethylamine for HPLC, hydrochloric acid, phosphoric acid, and potassium dihydrogen phosphate; Sigma-Aldrich, USA. Water was obtained using a Milli-Q purifier.

HPLC method development

To determine the percentages of drug in tablets and the drug released from the produced formulations, either fresh or stored, a stability indicating method was developed.

Mobile phase

1 ml of triethylamine was put into a 1000 ml measuring flask containing 900 ml of distilled water, mixed, pH adjusted to 3 by phosphoric acid, and the volume was completed with distilled water (solution I). Acetonitrile and solution I (30:70) were mixed. A Luna® C18 (5 µm, 25 cm, 4.6 mm) column and Waters HPLC equipment were employed for the analysis. At 254 nm, 20 µl were injected at 1 ml/min.

Standard solution preparation

100 mg of OM were accurately weighed and transferred into a 250-ml volumetric flask that contained 200 ml of the mobile phase. Then, the flask was placed on a magnetic stirrer for 60 minutes, or until it dissolved. Then, the volume was completed and mixed. Serial dilutions were done and then filtered through a 0.45 µm.

Test solution preparation

Twenty tablets were weighed, the average weight was computed, and then they were crushed. The weight of powder equivalent to 10 mg of OM was then transferred to a volumetric flask with a capacity of 250 ml. 150 ml of the mobile phase was added, put on a stirrer for 60 min, then, the volume was completed, mixed, diluted as required, and filtered through a 0.45 µm.

Validation of the developed HPLC

The validation was conducted per the ICH Guideline: Validation of Analytical Procedures (Q2 R1) (ICH, 2005) and the United States Pharmacopoeia (USP, 2019).

System suitability

Five injections of a standard solution at 100% strength were used to assess suitability. Its parameters were obtained from the HPLC equipment. The parameters were within the acceptance criteria present in the FDA guidelines (FDA, 2005).

Linearity

The linearity of OM was assessed in the range of 5-35 µg/mL. The standard curve was constructed, and the slope, y-intercept, and correlation coefficient (R2) were obtained.

Accuracy

The accuracy was performed by three replications of three concentrations (10 µg/mL, 20 µg/mL, and 25 µg/mL), and each strength was injected three times. Three spiked concentrations were prepared by adding 20%, 40%, and 50% to three 20 µg/ml, injected in triplicate, and the % recovery was computed (Hasan *et al*., 2023).

Precision

The repeatability and intermediate precision of the HPLC technique for OM were studied. Six assessments of the test concentration were used to measure repeatability. Six concentrations made by three distinct analysts each helped define the intermediate precision. The relative standard deviation percentage (RSD) was calculated. Intraday precision was performed by assessing the peak area of three OM solutions with a concentration of 5 µg/mL three times on the same day. Then, interday precision was administered on three different days, and RSD was assessed.

Specificity

The capacity to differentiate between the analyte(s) and the other components is known as specificity in analytical methods. Complete separation of the analyte peak(s) from other peaks originating from the matrix is what guarantees the HPLC method's accuracy. In order to assess specificity, 20 µl solutions of the standard, sample, placebo, and blank were each independently injected into the chromatographic apparatus (Le *et al*., 2019).

Robustness

The robustness was assessed by changing the flow rate and the wavelength, and RSD results should be less than 5% (Hasan *et al*., 2023; Surapuraju *et al*., 2022).

Stressed degradation

The degradation was carried out under stressful conditions. The sample was subjected to heat degradation by being heated to 100 °C for 1 h. Concerning hydrolytic degradation, 5 ml of 1 N HCL or 1 N NaOH solution were added to the sample and left for 1 h. The sample was then neutralised with NaOH or HCl, as appropriate, prior to HPLC analysis. Five milliliters of a 10% hydrogen peroxide solution were applied for one hour in order to assess oxidative degradation.

Tablets preparation

Olmesartan was co-ground with the superdisintegrant (Crospovione type A, Ac-di-Sol) and sieved before being combined with other substances using a geometrical approach, including calcium carbonate. The lubricant was then added. Using a single punch machine, tablets were compressed on a flat punch 8 mm into 200-mg [Erweka, Germany]. In Table I, the formulations are revealed.

Assessment of after compression characteristics

Variation of weight

From every formulation, 20 tablets were separately weighed [Sartorius, Germany]. The mean was estimated. The weight should be within the limit of 200 mg±7.5% (USP, 2019).

Content uniformity

The uniformity was assessed through crushing of 10 tablets from every formulation and testing the amount of OM percent in each one separately using the method that was made up. The limit should be from 85% to 115% (BP, 2022).

Friability

Weighing of 10 tablets of every formulation was performed and introduced in the friablator [Veego, India] at 25 rpm for 4 min. After brushing the tablets and weighing them again, friability was determined (USP, 2019).

Hardness

The hardness of ten tablets from each formulation was evaluated [Tablet Hardness Tester, Erweka, Germany]. Next, it was calculated in kilograms (Choursiya & Pandit, 2021).

Disintegration time

The USP disintegration tester [Veego, India] was employed to measure the disintegration time for six tablets of each formulation (USP, 2019; Choursiya & Pandit, 2021).

***In-vitro* dispersion time test**

A FDT from each formulation was dropped onto a ten-milliliter measuring cylinder after it had received six milliliters of distilled water. The time it would take for the tablet to reach complete disintegration into tiny pieces was calculated. The results of tests done on three pills of each formulation were given in seconds (Hari *et al*., 2018).

Table I. Formulae of OM fast dissolving tablets (Each tablet contains 40 mg *OM*, 2 mg aspartame, 2 mg banana flavor and 3 mg magnesium stearate)

Formula	Diluent	Disintegrant		
	Lactose fast flow (mg)	Calcium carbonate (mg)	Ac-Di-sol (mg)	Crospovidone (mg)
OD 1	137	----------	16	--------
OD 2	133	------	20	--------
OD 3	113	-------	--------	40
OD 4	93	-------	-----	60
OD 5	117	20	16	------
OD 6	113	20	20	-----
OD 7	93	20	-----	40
OD 8	73	20	--------	60
OD 9	97	40	16	--------
OD10	93	40	20	-----
OD11	73	40	----------	40
OD12	53	40	------	60

Wetting time

A Petri dish with a 10 cm diameter was filled with five tissue papers, adding ten millimeters of the water-soluble dye eosin. On top of the tissue, a tablet was delicately put. The time needed for water to reach the top surface was calculated (Hari *et al*., 2018).

Ratio of water absorption

A segment of tissue paper was bent twice, then put in a tiny Petri-dish with 6 ml of water to measure the tablet's ability to absorb water. A tablet was placed on the tissue. The wet tablet weight was then determined. The following equation was employed to compute the water absorption ratio (R), employing the following equation:

$$R = 10\left(\frac{Wa}{WB}\right)$$

Where Wb is the tablet weight prior to absorption of water; Wa is the tablet weight post water absorption (Rahane & Rachh, 2018).

***In-vitro* release studies**

The USP dissolution tester [Dissolution Apparatus Veego, India] was used to perform the release test in 0.05 M phosphate buffer (pH 6.8) at 37°C at intervals of 5, 10, 15, 20, and 30 min. Aliquots, each 5 ml in size, were taken from Apparatus II (paddle), which was rotating at a speed of 50 rpm (USP, 2019). The withdrawn samples were filtered, properly diluted, and subjected to an HPLC assay established for the detection of OM. In order to preserve sink conditions, comparable volumes of media were added to the dissolving media (Rahi *et al*., 2021).

Accelerated stability testing of tablets:

The chosen formulations were kept for 6 months at 40°C and 75% RH [Climacel Stability Chamber, Germany] (FDA, 2014; World Health Organisation, 1996). The stored FDTs were investigated for any alterations in colour and/or appearance and hardness, time to disintegrate, time of wetting, dispersion, and release, and analysed chemically by HPLC. After evaluation of the hardness, time to disintegrate, time of wetting, dispersion, and release after storage, Similarity factor (f2) in the following equation was utilised to compare the release data.

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

where n is the number of time points, R is the release value of the reference, and T is the release results of the test at time t (Alam *et al*., 2018).

Characterization of physical powders

The co-ground powder of the optimised FDT powder was characterised using DSC. DSC analysis for OM, and their co-ground powder was performed employing a DSC (Shimadzu DSC-60, Columbia, MD, USA). The samples (10 mg) were introduced in sealed pans of aluminium under nitrogen (20 ml/min) at a rate of 10 °C/min and in the range of 0-250 °C (Sid *et al*. 2021).

Statistical analysis

Calculations were made to determine the linearity RSD%, the limit of detection (LOD), and the limit of quantitation (LOQ) employing the GraphPad Prism 9® program. The calculated values of the obtained information, such as the mean, standard deviation (SD), and relative standard deviation

(RSD%), were analysed using the standards established by USP 43 and ICH. A one-way analysis of variance (ANOVA) was performed, and a 95% confidence interval was determined, in order to validate the linearity of the procedure that was suggested.

RESULTS AND DISCUSSION

To accurately determine OM, a new HPLC was developed. The suitability of the system is revealed (Table II), where the number of plates, tailing, and capacity factor were 6325, 0.57, and 6.74, respectively. The calibration curve and chromatogram (Figure 2 and 3) are linear over the range 5–30 µg/ml, where r, intercept, slope, and *p*-value were 0.999, 157030, 41368, and $1.5*10^{-6}$, respectively, and the developed HPLC was appropriate.

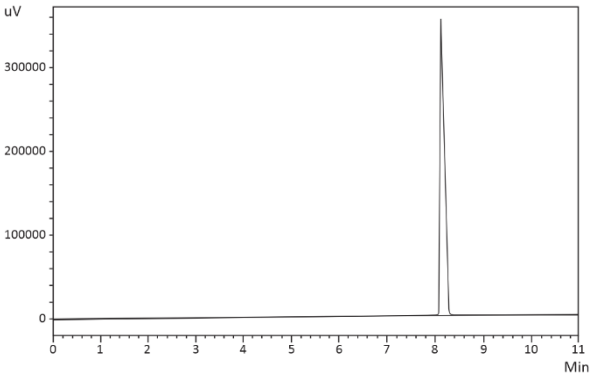

Figure 2. chromatogram of OM (concentration was 5 µg/ml, flow rate 1 ml/min at 254nm using the mobile phase).

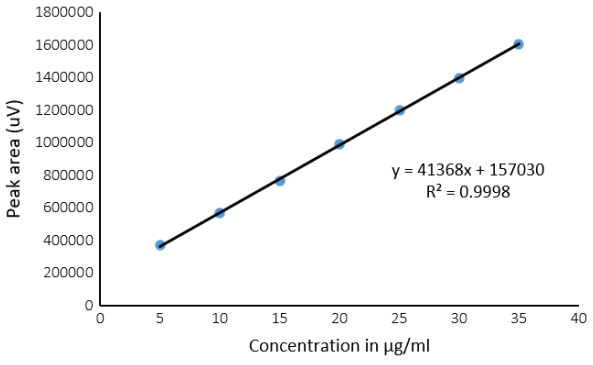

Figure 3. Calibration curve of OM.

The precision RSD (Table II) varied from 0.12 to 0.23, which was within the limit. Moreover, the accuracy was 98.43, and the SD was 0.51, indicating that the accuracy was good. In addition, the approach demonstrated good sensitivity, with LOD of 1.26 µg/ml and LOQ of 3.83 µg/ml, respectively. Regarding the specificity, no peaks appeared in the placebo, referring to any components of the tablets devoid of the drug at the retention time of OM (Table II). The recovery for 1 M HCL, 1 M NaOH, and 10% hydrogen peroxide, respectively, was around 88%, 92.5%, and 85%, while the degradation was not more than 15%. The robustness was evaluated by making slight changes in flow rate from 1 ml/min to 1.02 ml/min and 0.98 ml/min and wavelength to 253 nm and 255 nm, the RSD% results do not exceed 0.6%.

The physical characteristics of tablets, with weight variation results ranging from 196 to 202 mg within the pharmacopoeia's 7.5% limits (Table III). The hardness ranged from 4.1 to 7.4 kg/cm3 (with a minimum of 3 kg/cm3). The FDTs friability was promising since it did not exceed the limit of USP ≤1% (USP, 2019). The content uniformity of all formulations ranged from 96.1% to 99.4% within the BP limit (85%-115%) indicating that co-milling did not negatively affect the distribution of drug within each formula. Formulation dispersion times ranged from 40 to 59 s. Furthermore, the wetting time and water absorption ratio varied between 48 and 130 s and 40% and 149%, respectively. The formulations OD11–OD12 showed the optimum time and disintegrated within the range of 31–35 s. *In vitro* dispersion time, wetting time, and water absorption ratio of the formulations OD11–OD12 were the optimum; this may be due to the presence of 20% Crospovidone type A per tablet, attributed to the impact of Crospovidone resulting in quick enlargement and hydrostatic pressures forcing the tablet to disintegrate and the effect of swelling without forming the gel accelerating the water absorption (Sumaiyah *et al*., 2019; Hidayati *et al*., 2020).

The fastest release of OM Q_{10} was from OD11 and OD12 formulations, exceeding 90% within 10 min, while the dissolution of OM standard was 9.8% within the same time. This may be due to the co-milling with Crospovidone type A, which results in the particles being exposed to dissolving media more frequently (Figure 4). Crospovidone also improves the wettability of poorly soluble drugs (Dhakal *et al*., 2022). Formulations containing Ac-Di-Sol show a release of OM ranging from 75% to 85% after 10 min while the formula (OD9) releases 85% after 10 min. Moreover, calcium carbonate increases pH in order to increase the solubility of OM (Huang *et al*., 2022).

Table II. Validation parameters of analytical method.

Acceptance criteria		Results
Suitability n=5	Theoretical plates ≥ 2000	6325±0.52
	Tailing factor ≤ 2	0.57±0.04
	Capacity factor ≥ 2	6.74±0.01
Linearity	Correlation coefficient $R^2 \geq 0.98$	0.999
	Slope	157030
	Intercept	41368
	Regression equation	41368x + 157030
	p-value lower than 0.05	$1.5*10^{-6}$
	Range	5-30 µg/mL
Accuracy n=3	Mean % recovery (95% to 105%)	98.43 %
	RSD ≤ 2%	0.51%
Precision	Repeatability (RSD % ≤ 5%)	0.12%
	Intermediate precision (RSD % ≤ 10%)	0.23%
Sensitivity	LOD	1.26 µg /mL
	LOQ	3.83 µg /mL
Specificity	No peaks at retention time of the drug	No peaks
Stressed degradation n=3	Recovery % in 1 M HCl	88.14 % ± 0.39
	Recovery % in 1 M NaOH	92.31%± 0.11
	Recovery % in 10% H_2O_2	85.47 % ± 0.37
Robustness	RSD % at 1 mL/min	0.52%
	RSD % at 1.02 mL/min	0.31%
	RSD % at 0.98 mL/min	0.19%
	RSD % at 253 nm	0.29%
	RSD % at 254 nm	0.25%
	RSD % at 255 nm	0.32%

Table III: Physicochemical properties of the tablets (results are given as mean ± SD)

Formula	Tablet weight (mg)	Hardness (kg/cm3)	Disintegration time (s)	Drug content (%)	Wetting time (s ± SD)	Water absorption ratio (%) ± SD	*In vitro* dispersion time (s)	Friability (%)	Content uniformity
OD 1	201±0.15	5.1±0.75	70±1.56	99.89±0.82	130±0.0	40±0.31	110±0.55	0.21±0.12	98.1±1.5
OD 2	200±0.24	7.4±0.29	61±2.16	101.23±1.1	114±0.3	47±0.35	105±0.32	0.16±0.31	99.4±1.6
OD 3	202±0.51	5.9±0.67	64±1.19	99.39±1.31	112±1.2	43±1.22	143±0.25	0.14±0.26	97±1.7
OD 4	202±2.1	4.1±0.68	120±1.52	98.92±1.21	101±1.0	80±1.2	181±0.34	0.17±0.36	96.5±0.9
OD 5	197±2.5	5.3 ±0.18	135±1.47	99.0 ± 1.08	93±0.22	95±0.23	190±0.79	0.18±0.19	98.1± 1.8
OD 6	201±3.5	5.9±0.29	126±2.64	97.96±1.28	81±0.14	96±0.14	176±0.17	0.16±0.18	96.1±1.2
OD 7	196±0.54	4.3 ±0.15	50±1.13	98.09±1.07	74±0.11	110±0.51	118±0.23	0.24±0.16	97.4±1.6
OD 8	202±0.6	4.8 ±0.11	43 ±0.93	99.83±1.33	61±0.22	84 ±0.36	89±0.42	0.29±0.12	96±1.5
OD 9	198±0.39	6.1 ±0.21	46±0.22	100.14±0.5	50±0.14	140±0.12	96±0.21	0.24±0.25	97.5±1.5
OD 10	202±0.31	5.9±0.11	36±0.12	101±0.62	48±0.22	149±0.12	80±0.17	0.17±0.32	97.8± 1.3
OD 11	197±0.56	6.1 ±0.12	31±1.19	99.6 ± 1.58	93±0.22	110±0.23	64±0.79	0.21±0.19	96.5±1.2
OD 12	201±0.43	5.9±0.45	35±1.93	98.95±0.78	81±0.14	124±0.14	75±0.17	0.5±0.31	96.7±1.1

The formulas OD11 and OD12 showed promising dissolution and other characteristics, depending on all previous results concerning physicochemical characteristics and release comparing to the standard. So, OD11 and OD12 were chosen for a stability investigation.

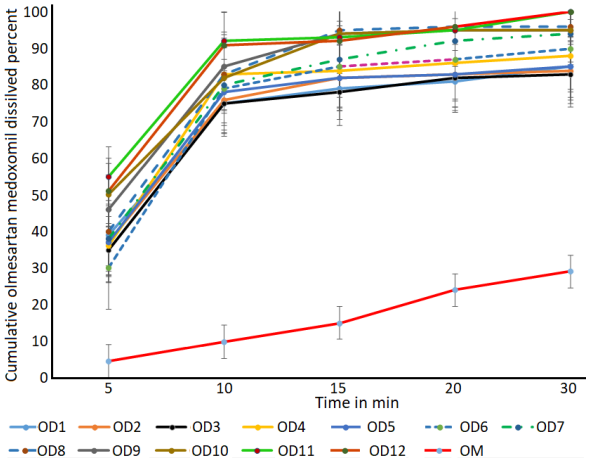

Figure 4. dissolution of OM from the prepared FDTs.

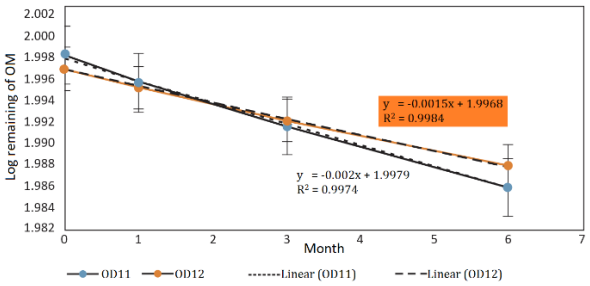

Figure 5: Stability of selected formulations at 40°C± 2°C / 75%± 5% RH

Within 6 months, none of the FDTs stored at 40°C (75% RH) exhibited any colour or appearance changes. The developed HPLC stability indicator assay was used to determine the percentage of remaining OM in OD11 and OD12 that degraded less than 3%, which was within ICH guidance. The selected formulations had log% remaining of 96.8 and 97.25% after 6 months of OD11 and OD12, respectively (Figure 5). The content of OM remains after the storage of the selected formulations (Figure 6A). The hardness of OD11 and OD12 decreased while their disintegration time increased. The moisture uptake by the disintegrant led such disintegrants to lose some of their absorption. and swelling properties, might be blamed for the rise in the disintegration time of all formulations. Similarity factor and ANOVA emphasise no significant impact of storage on the release of OD11 and OD12, where their similarity values were 74 and 76, respectively (limit ≥50).

The hardness of OD11 and OD12 (Figure 6B) decreased while their disintegration time increased (Figure 6C). It's important to notice that formulation OD 12 hardness was significantly reduced, while the time of wetting and dispersion of OD11 > OD12 (Figure 6D, E). The impact of storage on the release of OD11 and OD12 (Figure 6F, G), where the similarity factor was utilised and its values were 74 and 76, respectively.

Using the co-milling technique, no previous trials have improved OM dissolution. Comparing with the published studies of researchers trying to formulate OM in dosage forms, for instance, Karuna DS *et al.* (2014) formulated a combination of hydrochlorothiazide, OM, and amlodipine besylate tablets; the optimised formula showed a dissolution rate of 90% for hydrochlorothiazide, OM, and amlodipine besylate tablets within 30 minutes, while in our research the release was > 90% within 10 min. for OM in the formulations OD11 and OD12 within the same time frame. By creating solid lipid nanoparticles (SLNs), Arun *et al.* (2018) increased the availability of OM. Prepared SLNs were assessed physically and *in vivo* in rats. It demonstrated a > 4-fold improvement in dissolution when compared to OM nanosuspension (NS). As a result of DSC (differential scanning calorimetry) and XRD (X-ray), drug combinations in SLNs were revealed in amorphous form. Comparing the results of the bioavailability of SLN and NS, they were 7 and 3.5 times the drug, respectively. Furthermore, González *et al.* (2022) prepared OM tablets by the direct compression method of OM with microcrystalline cellulose and hypromellose, the release was 46% after 10 min, while our optimised formulations showed more than 90% after the same time.

DSC evaluated the characterization of co-milling of OM with crospovidone type A. The DSC curves for drug, crospovidone type A, and co-ground powder are shown in (Figure 7). The OM DSC curve revealed melting endotherm at 183.5°C (González *et al.,* 2022); crospovidone type A showed a decomposed broad melting point of 92.50 °C; and, in co-ground powder, the melting point of OM was shifted to 171.45 °C.

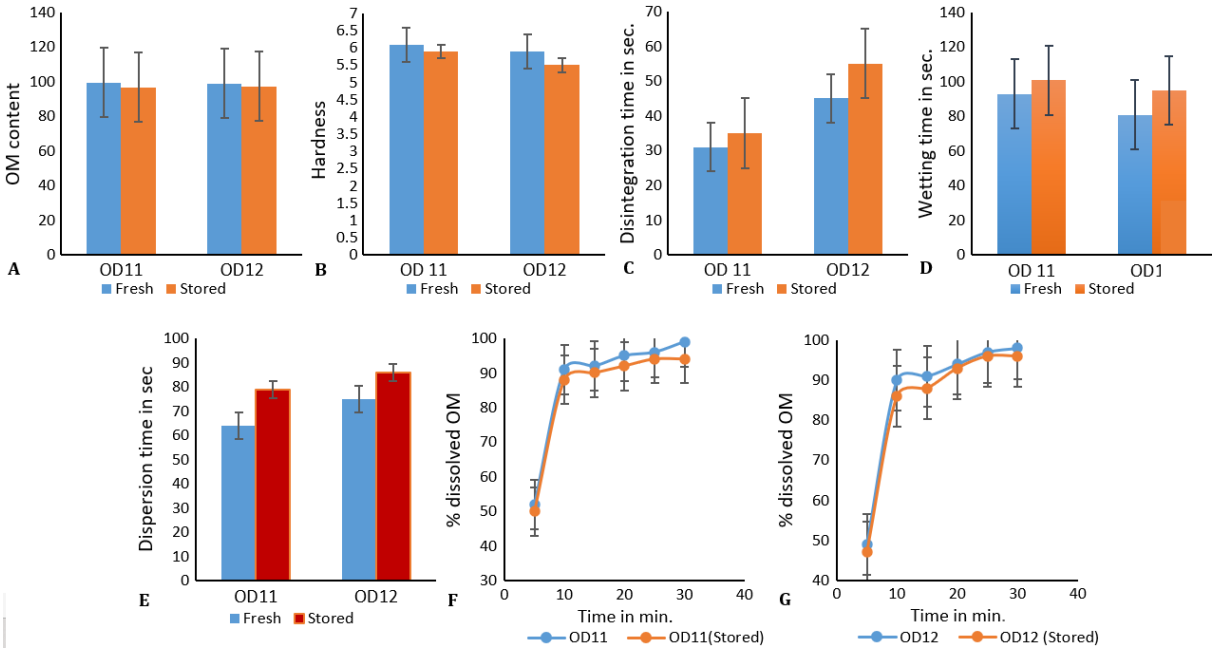

Figure 6. impact of storage on physicochemical characteristics of OM tablets. (A) Effect of storage on the content of the chosen formulations; (B) Impact of storage on the hardness values of the chosen formulations); (C) Impact of storage on the disintegration values of the chosen formulations;(D) . Impact of storage on the time of wetting values of the chosen formulations; and (E) Impact of storage on the dispersion of the chosen formulations, (F) Impact of storage on the time of release of OD11; and (G) Impact of storage on the release of OD12.

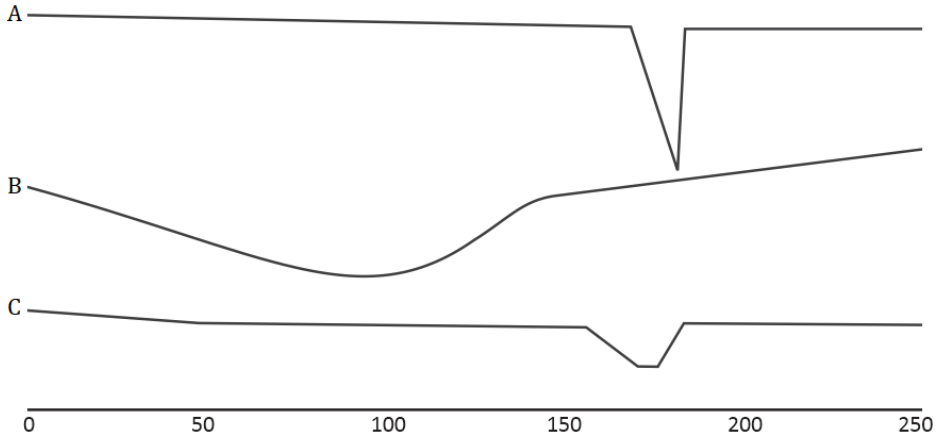

Figure 7. A) DSC of OM; B) DSC of Crospovidone; C) co-ground mixture of OM and Crospovidone.

However, the peak was broader, less sharp, and smaller compared with the peak of the pure OM, indicating reduced crystallinity of the drug during co-grounding and illustrating the characteristic peak of OM with lowered sharpness and intensity compared to the pure OM, revealing possible conversion to an amorphous state (Gaikwad & Avari, 2021). This may be a result of enhanced lattice defects in drug crystals (Arun *et al.*, 2018) and incomplete complexation (Sid *et al.*, 2021).

CONCLUSION

In this particular study, the solubility of OM was shown to be significantly improved after being co-milled, which was the methodology used. A co-milling approach using superdisintegrants and then mixing with the buffering agent (calcium carbonate) could enhance the dissolution of OM in the formulations OD11 and OD12 prepared with crospovidone type A and calcium carbonate. We can conclude that a more soluble complex was formed from OM and crospovidone type A, especially in the presence of a suitable buffering agent.

CONFLICT OF INTEREST

The authors wish to stress that there is no financial, personal, authorship, or any other type of conflict of interest associated with this research that may have an effect on the findings of the research.

REFERENCES

Alam, S., Bishal, A., & Bandyopadhyay, B. (2021). Formulation and evaluation of metformin hydrochloride sustained release matrix tablets. International Journal of Current Pharmaceutical Research. 82-88. https://doi.org/10.22159/ijcpr.2021v13i5.1899

Alan, S., Yu, L. & BChir, M.B. in Brenner and Rector's The Kidney, 2020

Al-Shdefat, R. (2020). Solubility determination and solution thermodynamics of olmesartan medoxomil in (PEG-400 + water) cosolvent mixtures. Drug Dev Ind Pharm., 46 (12), 2098-2104. https://doi.org/10.1080/03639045.2020.1847136

Arun, B., Narendar, D. & Veerabrahma, K. (2018). Development of olmesartan medoxomil lipid-based nanoparticles and nanosuspension: preparation, characterization and comparative pharmacokinetic evaluation, Artificial Cells, Nanomedicine, and Biotechnology, 46(1), 126-137. https://doi.org/10.1080/21691401.2017.1299160

Avari, J. & Gaikwad, S. (2021). Molecular Inclusion - Novel Approach to Enhance Solubility of Olmesartan Medoxomil Using Hydroxypropyl β Cyclodextrin (HP β -CD). Acta Pharmaceutica Sciencia. 59, 276-290. 10.23893/1307-2080.APS.05916.

Choursiya, A. & Pandit, D. (2021). Formulation and Evaluation of Fast Dissolving Tablets of Lansoprazole by Solubility Enhancement Technique. Current Research in Pharmaceutical Sciences, 11(2), 54-64. https://doi.org/10.24092/CRPS.2021.110203

Dhakal, B., Thakur, J.K., Mahato, R.K., Rawat, I., Rabin, D.C. & Chhetri, R.R., *et al*. (2022). Formulation of Ebastine Fast-Disintegrating Tablet Using Coprocessed Superdisintegrants and Evaluation of Quality Control Parameters. Scientific World Journal. 19, 9618344. https://doi.org/10.1155/2022/9618344

Eisa, M.A., El-Megrab, A.N., El-Nahas, M.H. (2022). Formulation and evaluation of fast dissolving tablets of haloperidol solid dispersion Saudi Pharm J. 30(11), 1589–1602. https://doi.org/10.1016/j.jsps.2022.09.002

FDA (November, 2014) Expiration Dating and Stability Testing for Human Drug Products. Retrieved on April 4, 2022 from https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-technical-guides/expiration-dating-and-stability-testing-human-drug-products

FDA (2005) Q2(R1) Validation of Analytical Procedures: Text and Methodology from Q2(R1) Validation of Analytical Procedures: Text and Methodology Guidance for Industry | FDA

González, R., Peña, M.Á. & Torrado, G. (2022). Formulation and Evaluation of Olmesartan Medoxomil Tablets. Compounds, 2 (4), 334-352. https://doi.org/10.3390/compounds2040028

Hari, K., Rajeswari, S. & Ramanamurthy, V.K. (2018). Preparation and Evaluation of Orally Disintegrating Tablets of Drotaverine Hydrochloride Using Sublimation Technique. Int J Pharm Pharm Sci, 10, 85-95. https://doi.org/10.22159/ijpps.2018v10i5.24503

Hasan, R., Begum, R., Huq, O., Rahman, N., Akter, S., Khan, HS., & Islam, F. (2023). Development of normal phase HPLC based method for the determination of retinyl palmitate in fortified edible oils, International Journal of

Food Properties, 26:1, 24-37, https://doi.org/10942912.2022.2151618

Husseiny, R.A., Abu Lila, A.S., Abdallah, M.H., El-ghamry, H.A. (2018). Fast disintegrating tablet of Valsartan for the treatment of pediatric hypertension: In vitro and in vivo evaluation, Journal of Drug Delivery Science and Technology, 43, 194-200. https://doi.org/10.1016/j.jddst.2017.10.014.

ICH. International Conference on Harmonization, Validation of Analytical Procedures: Text and Methodology, Q 2 (R1). ICH, 2005.

ICH Q1A (R2) Stability testing of new drug substances and drug products - Scientific guideline (2003)

Karuna, D.S., Sowjanya, L., Ubaidulla, U., Rathnam, G. (2014). Formulation and Evaluation of Triple Drug Combination of Olmesartan Medoximal, Amlodipine Besylate and Hydrochlorothiazide Tablets, International Journal of Advanced Pharmaceutics, 4(2),146-153.

Koike, H., Konse, T., Sada, T., Ikeda, T., Hyogo, A., Hinman, D., Saito, H. & Yanagisawa, H. (2003). Annual Report Sankyo Research Laboratories, 55: 1-91.

Le, T.H.H., Phung, T.H., Le, D.C. (2019). Development and Validation of an HPLC Method for Simultaneous Assay of Potassium Guaiacolsulfonate and Sodium Benzoate in Pediatric Oral Powder. J Anal Methods Chem. 7, 2019:6143061. doi: 10.1155/2019/6143061. PMID: 30984442; PMCID: PMC6431496.

Martindale: The Complete Drug Reference. London, UK: Pharmaceutical Press (2011).

Hidayati, N., Sulaiman, T & Nurhaini, R. (2020). Optimization formula of fast disintegrating tablets Ketoprofen β-cyclodextrin inclusion complex with sodium starch glycolate and crospovidone as the superdisintegrants. J Phys Conf Ser. 1517, 012047. https://doi.org/10.1088/1742-6596/1517/1/012047

Huang, Y., Cao, L., Parakhonskiy, B.V. & Skirtach, A.G. (2022). Hard, Soft, and Hard-and-Soft Drug Delivery Carriers Based on CaCO3 and Alginate Biomaterials: Synthesis, Properties, Pharmaceutical Applications. Pharmaceutics, 14, 909. https://doi.org/10.3390/pharmaceutics14050909

Rahane, R.D. & Rachh, P. (2018). A review on fast dissolving tablet. Journal of Drug Delivery and Therapeutics. 8, 50-55. https://doi.org/10.22270/jddt.v8i5.1888

Rahi, F.A., Mohammed, M.S & Fayyadh, M.S. (2021). Linagliptin and gliclazide di-loaded extended-release nanoparticles: formulation and evaluation. Wiad Lek, 74 (9 cz 2):2315-2322. https://doi.org/10.36740/WLek202109212

Saab, M. & Mehanna, M.M. (2019). Disintegration time of orally dissolving films: various methodologies and in-vitro/in-vivo correlation. Pharmazie, 74(4), 227-230. https://doi.org/10.1691/ph.2019.8231

Sid, D., Baitiche, M., Elbahri, Z., Djerboua F., Boutahala, M., Zouhair Bouaziz & Marc Le Borgne (2021) Solubility enhancement of mefenamic acid by inclusion complex with β-cyclodextrin: in silico modelling, formulation, characterisation, and in vitro studies, Journal of Enzyme Inhibition and Medicinal Chemistry, 36, 605-617, DOI: 10.1080/14756366.2020.1869225

Sumaiyah, S., Mentari, J. & Suryanto S. (2019). The Effect of Crospovidone on the Dissolution Profile of Amlodipine Besylate from Fast Orally Dissolving Film. Open Access Maced J Med Sci., 7, 3811-3815. https://doi.org/10.3889/oamjms.2019.510.

Surapuraju, P.K.R., Raveendra, Reddy, Juturu, R.R. (2022). Development, Robustness by Design Expert and Validation of a Method for Enantiomeric Impurity Content Determination in Pretomanid Drug Substance and Pharmaceutical Dosage Form, *Journal of Chromatographic Science*, 2022, bmac090, https://doi.org/10.1093/chromsci/bmac090

The Pharmacopoeia of United States of America", 43th Ed., National Formulary 38, Mack publishing Co. Easton, vol. 2, Electronic version (2019).

The British Pharmacopoeia", british pharmacopoeia commission office, London (2022). https://www.pharmacopoeia.com.

World Health Organization (1996) Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. Retrieved on April 4, 2022 from https://www.paho.org/hq/dmdocuments/2008/6_Annex_5_report_34.pdf

Vaughan, A.S., Coronado, F., Casper, M., Loustalot, F. & Wright, J.S. (2022). County-Level Trends in Hypertension-Related Cardiovascular Disease Mortality-United States, 2000 to 2019external icon. *J Am Heart Assoc,* 11(7), e024785. https://doi.org/10.1161/jaha.121.024785