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Research Article:

Evaluation of Hydrotropic Freeze Dried Systems for Meloxicam Solubility Enhancement

Rasha Khalid Shakir, Amina Mudhafar Al-Nima, Shahad Myasar Alfaris, Omar A Hamid

Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq.

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Abstract

Background: The low solubility of Meloxicam (MX) necessitates preformulation strategies like hydrotropism to enhance it solubility and dissolution rate. Oral dispersible tablets (ODTs) give an alternative for patients with difficulty in swallowing, improving compliance and bypassing the first-pass effect. Many ODT manufacturing techniques, including lyophilization, aim to optimize MX's therapeutic performance. **Methods:** Five physical mixtures were prepared in five different ratios of MX to excipients (HPMC-E15, glycine, sodium benzoate, poloxamer-188 and mannitol). Comparative solubility analysis of (MX) was also conducted using different concentrations of different hydrotropic agents (sodium benzoate, sodium acetate, and urea). MX ODTs were prepared via lyophilization using mannitol as the matrix former and glycine as a protectant. The optimal formulation was selected and enhanced with a hydrotropic agent to improve MX solubility. Tablets were evaluated for physical properties, disintegration, dissolution, and drug content uniformity to ensure pharmacopeial compliance. In addition to FTIR and DSC tests which were conducted on the selected (MX) oral dispersible tablet formulation. **Results:** Solubility analysis identified sodium benzoate (30% m/v) as an effective hydrotropic agent for (MX) solubilization, facilitating the formulation of lyophilized tablets. After multiple trials incorporating HPMC-E15, Carbomer-934, Poloxamer-188, and mannitol as a diluent, three formulations (F5, F9, and F10) exhibited acceptable characteristics post-lyophilization. Among them, F5 (HPMC-E15 3%, Poloxamer-188 1%) demonstrated superior performance and was subsequently modified to F11 by incorporating 30% sodium benzoate to assess its impact on MX dissolution. One-way ANOVA of the drug release profile at 2 minutes indicated a significant enhancement, with F11 achieving 40.4±2.9% release compared to 18.6±1.9% for F5. **Conclusion:** The F11 demonstrated an enhanced dissolution rate, indicating the positive effect of the hydrotropic agent (sodium benzoate) on the solubility of MX.

1. Introduction

Poor bioavailability is an important problem for nearly half percent of newly discovered chemical entities, which necessitates the administration of drugs in a higher dose than needed to achieve better performance or the substitution of an oral route by another one like injection (1). Therefore, to design any pharmaceutical product, the importance of solubility must be considered, because it has an impact on the bioavailability of the drug. For orally administered dosage forms, the drug must be soluble in gastro-intestinal fluids and diffuse membranes to reach the bloodstream. Also, solubility affects on development outlook, and it is an important issue for most of the active pharmaceutical ingredients (APIs) which are isolated by crystallization processes in the field pharmaceutical industry (1,2).

Meloxicam (MX) is a selective inhibitor of cyclooxygenase 2 (COX-2) and a member of non-steroidal anti-inflammatory drugs (NSAIDs), that can be considered the cornerstone in the management of rheumatic inflammation symptoms, in which their goal is to relieve the pain and produce their

*Corresponding author: *Rasha Khalid Shakir, Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq.*
Email: rasha.kh@uomosul.edu.iq

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action as fast as possible (3,4). Unfortunately, MX has unstable and variable bioavailability due to its low solubility and wettability in water (12 µg/mL), thus its belongs to the Biopharmaceutical Classification System (BCS) class II, in which dissolution rate is a limited process and therefore the onset of action usually delayed (5,6).

On the other hand, rheumatoid arthritis is most common in geriatric people and at this age, people usually have dysphagia which is considered a problem in tablet intake compliance (7), therefore, several pieces of research and trials have been attempted to improve MX characteristics including solubility, its bioavailability and patient compliance.

Hydrotropism is a solubilization process where the addition of an excess amount of solute results in an increase in the aqueous solubility of the other poorly soluble one. How therapeutic drug solubility is improved by the effect of this process has been the focus of many analysts and chemists in the pharmaceutical analysis field. The mechanisms behind this process may be due to the self-aggregation potential, the structure breakers and the structure makers, and the formation of the micelles (8).

Moreover, an oral dispersible tablet (ODT) was considered as an alternative for those patients with difficulty in swallowing the conventional tablet (9) and was described by the European Pharmacopeia as a "solid preparations intended either to be placed in the mouth or to be dispersed or dissolved in water before administration" (10,11).
The ODTs' popularity has increased as they merge the advantages of solid and liquid formulas, they can dissolve in mouth saliva rapidly without the need for water to swallow, which increases their compliance, especially in the elderly, small age and mentally retarded population. In addition, the first passed effect is also reduced (10–12). Various techniques have been employed in the formulation of ODT including moulding, compression, melt granulation, phase transition, electrospinning, sublimation, effervescent, freeze drying (lyophilization), and spray drying methods (10,12,13).
Freeze drying is the most utilized technique to perform ODTs for many drugs that are available on the market nowadays. Freeze-dried ODTs which are also called oral lyophilizes demonstrate light construction and high porosity, thus, they disintegrate quickly (9). This process produces ODT by sublimation of water that's available in the formula mixture (10,14). It depends on three steps: deep freezing of drug suspension/solution, then removal of water from the preparation under low temperature during primary and secondary drying stage (9).

In this research, different hydrotropic agents (sodium benzoate, sodium acetate, and urea) were tried to improve the solubility of MX, in addition to that MX ODTs were formulated by lyophilization method in combination with the hydrotropic technique as a mean to improve the solubility of the drug within the tablets.

2. Materials AND Methods

2.1. Materials

The pure MX powder was sold from Apex pharma, Egypt. Sodium benzoate from Reagent World, USA. Urea and sodium acetate were obtained from Scharlau, Spain. Mannitol was gotten from Apollo Healthcare Resources. Poloxamer-188 was purchased from BASF, Germany. Glycine 99% was obtained from DAEJUNG, Korea. Hydroxy propyl methyl cellulose E15 (HPMC-E15) was received from Ashland Industries, Europe GMBH. Sodium hydroxide from Scharlab S.L., Spain. Potassium dihydrogen orthophosphate was taken from BDH Chemicals Ltd Poole, England. Anhydrous disodium hydrogen orthophosphate, from Dorset, SP79PX, UK. Carbomer-934 was obtained from HIMEDIA, India.

2.2. Methods

2.2.1 Characterization of drug and excipients

2.2.1.1. Fourier Transform Infra-Red (FTIR) spectroscopy

During the preformulation study, the FTIR spectra of MX pure powder, each of the individual excipients and the physical mixtures of drug with each excipient in ratios of (1:0.66, 1:1, 1:15, 1:2 and 1:22) by using several excipients (HPMC-E15, glycine, sodium benzoate, poloxamer-188, and mannitol respectively), in addition to the optimum formula were recorded on FTIR spectrometer (Shimadzu 8300, Japan) using KBr discs method at a scanning range of 4000-500 cm^{-1} (15).

2.2.1.2. Differential scanning calorimetry (DSC)

Samples of MX pure powder, each of the individual excipients and the physical mixtures of drug with each excipient (in the same above ratio for the FTIR study), in addition to the optimum formula, were sealed in aluminium pans then heated at a rate of 10 °C/min, over a temperature up to 350 °C under a nitrogen flow of 50 mL/min, using differential scanning calorimeter (Shimadzu DSC-60) (16).

2.2.1.3. Comparative solubility analysis

MX saturated solubility was measured in solutions containing varying hydrotropic agent types and concentration to select the best solubilizing hydrotropic agent or hydrotropic agents' combination. Excess amount of MX was added individually to 50 mL flasks that contained 25 mL of each 20% (m/v) and 30% (m/v) of aqueous solutions of each of the three different types of hydrotropic agents: sodium benzoate, sodium acetate, and

urea. In addition to the hydrotropic agents mixtures, including 10% Urea and 20% sodium benzoate solution that would be selected (17,18). After stirring for about 6 hrs, the resulting preparations were allowed to equilibrate for 24 hrs at 25 ℃, then filtered through whatman filter paper grade 41 (19,20), suitably diluted, and analyzed spectrophotometrically at 380 nm using UV- visible spectrophotometer (Labomed UVD-3000, USA) and phosphate buffer (pH 6.8) as a blank to determine the solubility of the drug in each sample. Each experiment was performed in triplicate and the enhancement ratios in solubility were calculated (17,18).

2.3. Preparation of MX ODTs by lyophilization technique

The MX ODTs were prepared using mannitol as a matrix former in three different concentrations 60%, 70%, and 90% (m/v). Glycine was used as a collapse protectant in a range of concentrations 1%, 1.5%, 0.2%, and 0.5% (m/v). Various polymers and concentrations were tested such as HPMC-E15: 1%, 2%, and 3% (m/v), poloxamer-188: 1% (m/v), and carbomer-934: 0.5% and 3% (m/v) (21) as shown in Table 1. First, a precise amount of the selected polymer in each formula was weighed and dissolved in distilled water with continuous stirring in a magnetic stirrer (Fisher Scientific, Korea) until dissolved. Then the required amount of MX, glycine, and mannitol was added and dispersed to get 7.5 mg of the drug per 0.5 mL of the resulting suspension. Using a PVC blister pack, with a 3 mm cavity depth and a diameter of 13 mm, 0.5 mL of the resulting suspension was poured then frozen at about -70 ℃ in a lyophilizer (OLABO, China) for about 2 hr, and lyophilized for about 24 hr at a temperature of less than -50 and pressure drop of less than 10 Pa, as shown in **Figure 1**: A, B, C. The best formula was selected depending on tablet properties, and taken to the next stage, which involves the addition of the selected hydrotropic agent to enhance the solubility of MX, as illustrated in **Figure 1**: D (16).

2.4. Selection of MX ODT with hydrotrope incorporation

The selected type and concentration of a hydrotropic agent, based on solubility data, was used to solubilize MX and formulate the lyophilized tablet (7.5 mg). First, 0.75 g of MX was dissolved in 35 mL of aqueous hydrotropic solution (containing 15 g of the selected hydrotropic agent) with continuous stirring for 6 hr by magnetic stirrer, then allowed to equilibrate for about 24 hr at 25 ℃. On the other hand, 10mL solution containing the required amount of mannitol (45 g), HPMC-E15 (1.5 g), poloxamer-188 (0.5 g), and glycine (0.75 g) were added to the aqueous hydrotropic solution of MX and the volume was completed with distilled water to 50 mL, to get 7.5 mg of MX in each 0.5 mL of the solution, 30% of the hydrotropic agent, 90% of mannitol, 3% of HPMC-E15, 1% of poloxamer-188, and 1.5% of glycine in the aqueous solution, with continues stirring until homogenized. Later, 0.5 mL of the resulting preparation was poured using the same previous type of PVC blister pack and frozen at about -70 ℃ in the lyophilizer for nearly 2 hr, lyophilized for about 24 hr at a temperature of less than -50 and pressure drop of less than 10 Pa (17).

Table 1. Composition of meloxicam oral dispersible tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Meloxicam (mg)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Mannitol (mg)	300	350	450	450	450	450	450	450	450	450	450
HPMC-E15 (mg)	5	5	5	10	15	-	-	-	-	2.5	15
Poloxamer-188 (mg)	5	5	5	5	5	5	5	-	-	-	5
Carbomer-934 (mg)	-	-	-	-	-	15	2.5	2.5	2.5	2.5	-
Glycine (mg)	5	5	5	5	7.5	7.5	7.5	7.5	1	2.5	7.5
Sodium benzoate (mg)	-	-	-	-	-	-	-	-	-	-	150

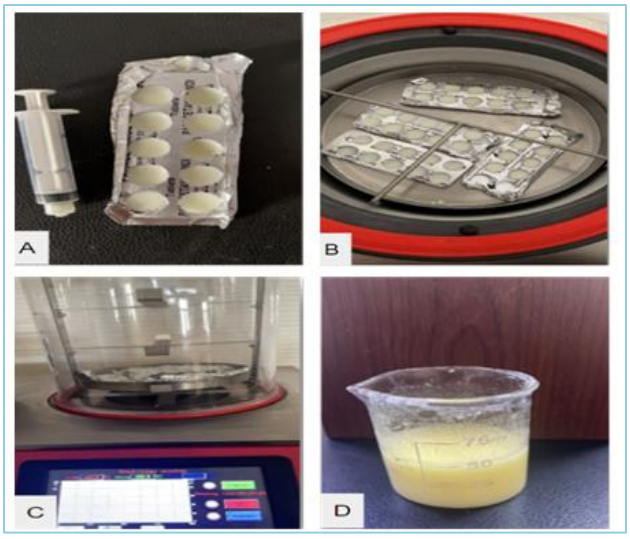

Figure 1. Preparation of meloxicam oral dispersible tablets by lyophilization technique, (A): measuring the required volume of the preparation inside the blister, (B): deep freezing of the sample, (C): freeze-drying the sample, (D) incorporation of the selected hydrotropic agent to the best formula to be lyophilized.

2.5. Evaluation of the prepared MX ODTs

2.5.1. Hardness

The hardness was determined for 10 tablets from the selected formulas, using (YD-1, Lpmie, and China hardness tester). The results were recorded in Newton, mean, and standard deviation was calculated (22).

2.5.2. Thickness and diameter

Ten tablets from the selected formulas were measured for thickness and diameter using a digital micrometre calliper (Ditron, China) (23).

2.5.3. *In-vitro* disintegration test

In this test, six tablets were used using the USP disintegration test apparatus (BJ-2 Huanyu, China) and 900 mL of phosphate buffer (pH 6.8) as a medium, at 37± 0.5 ℃. The time was measured in seconds for the tablets to be completely dispersed and it was recorded as disintegration time (16).

2.5.4. Content uniformity and weight variation

In this test, ten tablets of the selected formulas were crushed and dissolved by adding 5 mL of 0.1N NaOH, and 5 mL of methanol. The volume was then adjusted to 75 mL using phosphate buffer (pH 6.8) under continuous agitation, the solution was then filtered using a 0.45 µm filter and analyzed spectrophotometrically at 380 nm by UV- visible spectrophotometer (Labomed UVD-3000, USA) with phosphate buffer serving as a blank. The results are acceptable if the means of drug content fall within the range of 85–115% (16,24). Weight variation was determined by individually weighing 20 tablets and comparing each weight to the average weight of the ODTs using an electronic balance (Adam Equipment, PW 124, UK) (23,25).

2.5.5. *In-vitro* dissolution test

The MX release from the lyophilized tablets was determined by using the USP dissolution test apparatus type II (Copely, UK) of paddle type at 50 rpm and 37± 0.5 ℃. Phosphate buffer (pH 6.8) was used as dissolution medium, 5 mL of the sample was withdrawn at 1, 2, 4, 6, 8, 10, 15, 20, 25, and 30 min intervals and replaced with fresh medium. The samples were filtered using a 0.45 µm filter and then assayed spectrophotometrically at a wavelength of 380 nm. The experiment was repeated in triplicate (16).

2.5.6. Statistical Analysis

The Microsoft Excel 2016 using ANOVA (one-way analysis of the variance) was used for statistical analysis, the difference was statistically significant when $P<0.05$ and non-significant when $P>0.05$. Mean and standard deviation was used to express the values in the data.

3. Results and Discussion

3.1. Characterization of drug and excipients

3.1.1. Fourier Transform Infra-Red (FTIR) spectroscopy

FTIR chart of MX alone showed the following characteristic peaks: N-H of the secondary amid at 3431 cm-1, phenolic O-H at 3289 cm−1, C=O of the amide at 1619 cm−1 and both 1364, 1265 cm−1 for (O=S=O). These characteristic peaks appear in FTIR spectra of MX in its physical mixtures with the other peaks belonging to the functional groups of the additives. This indicates the absence of any significant interactions that may be happened as shown in **Figure 2**.

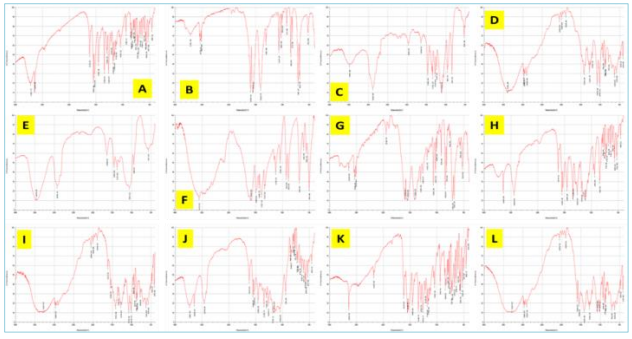

Figure 2. FTIR of meloxicam alone (A), sodium benzoate (B), poloxamer-188(C), mannitol (D), HPMC-E15 (E), glycine (F). Physical mixtures of meloxicam and sodium benzoate (G), poloxamer-188 (H), mannitol (I), HPMC-E15 (J), and

glycine (K). F11 is the prepared and selected formula of meloxicam oral dispersible tablet (L).

3.1.2. Differential Scanning Calorimetry (DSC)

The pure MX displays a high melting point of about 255 ºC (26), and its DSC thermogram exhibited an endothermic peak at 258.65, confirming its purity and crystalline structure. The endothermic peak appears narrow and deep, suggesting that during the melting process, the temperature remains constant. The endothermic peak is followed by an exothermic peak, indicating the transformation of the drug as given in Figure 3(A); these results are consistent with previous studies (27).

In addition to the pure drug, DSC was also performed for the other excipients and their physical mixtures with the drug to ensure that there are no interactions. Sodium benzoate doesn't reveal any peak, since it has a high melting point of greater than 400 ºC, and the used differential scanning calorimeter (Shimadzu DSC-60) provides a temperature up to 350 ºC (28). Poloxamer-188 shows the endothermic peak at 58.24 ºC (29), and mannitol at 170.69 ºC (9). HPMC-E15 as cellulosic derivative displays a wide endothermic peak at 88.92 ºC (27), and finally glycine at 259.41ºC as shown in Figure 3: B-F (30).

The DSC thermograms of the physical mixtures of MX and other excipients as illustrated in Figure 3 (G-K), indicate no significant change in the melting point of MX in the presence of excipients, denoting no interaction between them, except in the case of the physical mixture of MX and mannitol, in which melting endothermic events of the DSC thermogram shifted at a lower temperature for MX with weakness of the peak, because of the weak intermolecular bonds that resulted from mixing of MX and mannitol, which denotes physical interaction, rather than incompatibility as FTIR results showed no chemical interaction between them (9).

The DSC thermogram of the accepted formula of MX ODTs (F11) displayed a sharp endothermic peak related to mannitol crystalline melting, as mannitol content will determine the physical state of mannitol after freeze drying, not the amorphous or crystalline nature of other constituents (31). The endothermic peak of MX disappeared completely, suggesting that MX was changed to an amorphous state as illustrated in Figure 3 (32).

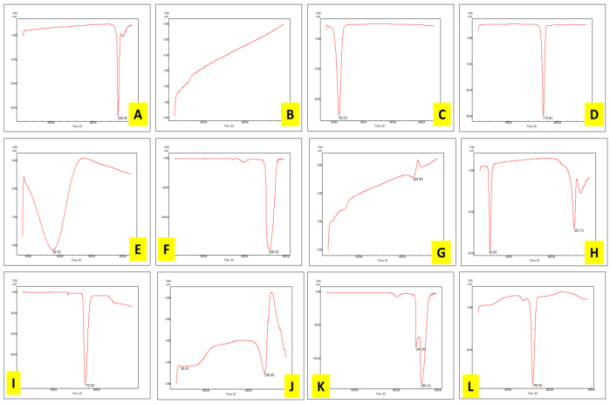

Figure 3. DSC of meloxicam alone (A), sodium benzoate (B), poloxamer-188 (C), mannitol (D), HPMC-E15 (E), glycine (F). Physical mixtures of meloxicam and sodium benzoate (G), meloxicam and poloxamer-188 (H), meloxicam and mannitol (I), meloxicam: HPMC (J), meloxicam and glycine (K). F11 is the prepared and selected formula of Lyophilized meloxicam oral dispersible tablet (L).

3.2.3. Comparative Solubility Analysis

Previous studies have shown that increasing hydrotrope concentrations enhances the aqueous solubility of poorly soluble drugs (18,19). In this study, the saturation solubility of MX was evaluated across various hydrotropic media, and enhancement ratios were calculated relative to distilled water. The hydrotropic medium composed of 10% urea and 20% sodium benzoate showed the highest solubility enhancement ratio of MX (Table 2) and therefore it was was selected to formulate a lyphhilized tablet of MX. All hydrotropic solutions improved MX solubility compared to distilled water, with enhancement observed in the order: sodium benzoate > urea > sodium acetate. At 20% m/v, the enhancement ratios were 7, 2.87, and 1.9-fold, respectively, while at 30% m/v, they reached 30, 3, and 2-fold. These outcomes align with reports by Jyotsana et al. (2017) and Maheshwari et al. (2007), who demonstrated similar trends in solubility improvement using hydrotropic dispersions of gliclazide and sodium benzoate for NSAIDs, respectively. The enhanced solubility of MX may result from both molecular interactions between hydrotropes and the drug, and self-association of hydrotrope molecules (33). Although the precise mechanism remains unresolved, Poochikian and Gradock's hypotheses offer a plausible explanation for observed differences among hydrotropes. While the mixed system (10% urea + 20% sodium benzoate) achieved a 10.5-fold increase, it was less effective than 30% sodium benzoate alone. This contrasts with findings by Maheshwari and Indurkhya (2010) using aceclofenac, highlighting the formulation-specific nature of hydrotropic enhancement. Accordingly, 30% sodium benzoate was selected for further development due to its superior solubilizing performance.in aqueous solubility was 120, 80, and 110 respectively when compared to their solubilities in distilled water, and the effect of this hydrotropic agent on solubilities of these drugs was negligible in phosphate buffer pH 8.2 (34). Solubility of MX was higher in the

presence of one type of hydrotrope over the other type, this can be demonstrated based on Poochikian and Gradock's explanation (35,36). To decrease the concentration of the individual hydrotropes, and to get better enhancement in solubility of MX, mixtures of urea and sodium benzoate were used in a concentration of 10%, and 20% respectively (37). However, the enhancement in solubility (10.5 times) was less than that of 30% sodium benzoate, the result was inconsistent with that obtained by Maheshwari and Indurkhya, 2010, who formulate and evaluate aceclofenac injection made by mixed hydrotropic solubilization technique (17). Therefore, sodium benzoate 30% wasselected for further formulation because it resulted in maximum solubility enhancement.

Table 2. Saturation solubility of meloxicam in different media (Distilled water, 20% and 30% sodium benzoate; 20% and 30% urea solution; 20% and 30% sodium acetate; a combination of 10% and 20% sodium benzoate)

Medium type	Solubility of Meloxicam (mg/mL) (n=3)	Solubility enhancement ratio
Distilled water	0.118±0.13	-
20% Sodium benzoate solution	0.83±0.14	7
20% Urea solution	0.334±0.11	2.87
20% Sodium acetate solution	0.21±0.06	1.9
30% Sodium benzoate solution	3.55±0.17	30
30% Urea solution	0.363±0.05	3
30% Sodium acetate solution	0.245±0.21	2
10% Urea and 20% sodium benzoate solution	1.24±0.25	10.5

3.2. Preparation of MX ODTs by lyophilization technique

Different trials were conducted to obtain tablets with accepted characteristics as illustrated in **Figure 4**. Three types of polymers were used in the MX ODTs formulation, including carbomer and HPMC as a binder, and poloxamer as a stabilizer. The working concentrations of the polymers were in the following ranges: 0.75-3%, 2-5% and 1-2% w/w respectively. Except for F5, F9, F10, and F11, all the formulas were unaccepted as shown in Figure 4. In the first four (F1, F2, F3, and F4) exhibited failure of forming tablet, which could be due to an insufficient amount of mannitol, glycine, and binders. However, increasing the concentrations of these agents resulted in a clear improvement in the Formulation as in F5 formula. On the other hand, replacing HPMC-E15, with the same concentration of carbomer-934 (3%) to act as a suspending agent in the formula F6 (38), resulting in a very thick mass. The concentration of carbomer-934 was lowered to 0.5% in F7 to get a suspension of the drug, but after the addition of 1% poloxamer-188 to the suspension, it lost its consistency and the thickening property of carbomer-934. After excluding poloxamer-188 in the formula F8 and using the same concentration of carbomer-934 (0.5%) and glycine (1.5%), a thick mass was formed as a result, which needed a decreased concentration of glycine to get accepted F9, and F10 formulas.

In addition to that, the primary drying temperature cannot be selected precisely during the process of freeze drying, since that required examining the formulation components using freeze drying microscopy in addition to DSC, to provide information about crystallization, collapse and other thermal events, that may affect the characteristics of the resulting tablets from the formulations.

3.3. Selection of MX ODT with hydrotrope incorporation

The best formula (F5) was selected as a lyophilized tablet, depending on physical properties , it was an intact tablet with good hardness and disintegration . The hydrotropic agent, sodium benzoate 30% (m/v) was chosen to be added to solubilize MX and formulate the lyophilized tablet of MX (7.5 mg) since it has the greatest solubility enhancement ratio (30) among the other hydrotropic types and concentrations. From the formulas (F1-F11) that were tried to formulate MX orally dispersible tablets, only four met the required standards (F5, F9, F10, and F11). In addition, F5 was selected to be taken for further studies, which involved the addition of the hydrotropic agent to enhance the solubility of MX. Based on solubility data from Table 1, 30% sodium benzoate (m/v) was found to be the most effective in increasing the solubility of MX, with a solubility enhancement ratio of 30 compared to distilled water. Consequently, sodium benzoate was selected to solubilize MX and was incorporated into the formulation of lyophilized tablets (F11) containing 7.5 mg of MX.

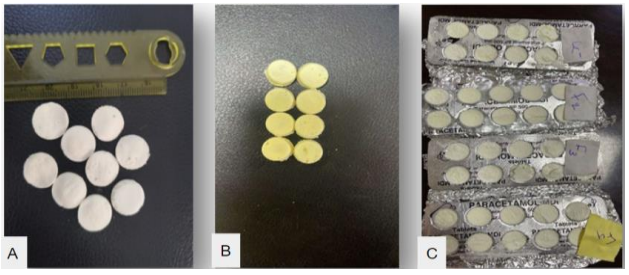

Figure 4. The resulting meloxicam orally dispersible tablets, (A) Accepted formula of meloxicam orally dispersible tablets (F5), (B) Orally dispersible tablets of meloxicam with the hydrotropic agent sodium benzoate 30% (F11), (C) Unaccepted formulas.

3.4. Evaluation of the prepared MX ODTs

3.4.1. Hardness

The hardness for the accepted formulas (F5, F9, F10, F11) was in the range of 1.56±0.55 to 39.2 ±15.9 newton. There is a significant difference in hardness between F5 and F11 ($p<0.05$), and no significant difference in hardness between F5, F9, and F10 ($p>0.05$) as given in Table 3 and Figure 5. The hardness of the tablets from the formulas F5, F9, and F10 indicated that there was no statistical difference between them since they have the same type and concentration of the diluent mannitol, although the type and concentration of the polymer used as a binder were different between them (3% HPMC-E15 with 1% poloxamer-188 in F5, 0.5% carbomer-934 in F9, 0.5% HPMC-E15 with 0.5% carbomer-934 in F10). However, when the hydrotropic agent 30% sodium benzoate was added to the F5 formula to get F11, the hardness was greatly increased to reach 39.2 ±15.9 newton ($p<0.05$), due to the presence of this high melting point hydrotropic agent, as illustrated in **Figure 5**, **Table 3** (39).

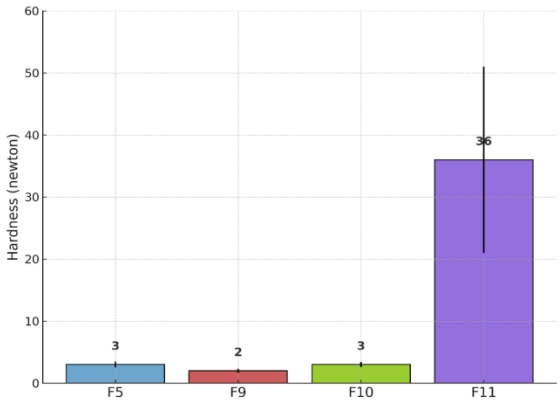

Figure 5. Hardness of the accepted formulas of meloxicam orally dispersible tablets

3.4.2. Thickness and diameter

The thickness and diameter of the tablets from the accepted formulas (F5, F9, F10, and F11), as illustrated in Table 3, were according to the dimensions of the pocket of the blister used and the nature of the materials involved in the formulas.

3.4.3. *In-vitro* disintegration test

The disintegration time of the accepted formulas F5, F9, F10, and F11 was in the range of 14.6± 3.5 to 96±20.8 sec. It can be ranked in descending order as F11> F10>F9>F5. There was no significant difference in disintegration time between F9 and F10, F9 and F5 ($p>0.05$), but the difference was significant between F11 and F5, F9, F10 also between F5 and F10 ($p<0.05$) as illustrated in Figures 6 and 7, and Table 3. The disintegration time of the accepted formula F5 (14.6± 3.5 sec) is lower than that of the formulas F9 (21.6±3 sec) and F10 (26.12±1 sec) since F5 contained a greater amount of glycine (1.5%), which enhance its disintegration time because this agent acts both as a bulking agent that gives elegance to the tablet and disintegration accelerant when compared with F9, and F10 which contained only 0.2%, and 0.5% of glycine respectively (38). In addition to that, F5 contained poloxamer-188 (1%), a polymer which was used as a stabilizing agent for the preparation of such lyophilized tablet (38), which also gave wetting and disintegration effect in this formula (40), while both F9 and F10 had the polymer carbomer-934 that may affect negatively on the disintegration of the tablets from these formulas (41). On the other hand, it seems clear that the presence of the hydrotropic agent sodium benzoate affects negatively on the disintegration time of the formula F11 ($p<0.05$), since the hardness of the tablet, increased due to the presence of this agent (39), as given in Figure 6 and 7, and Table 3.

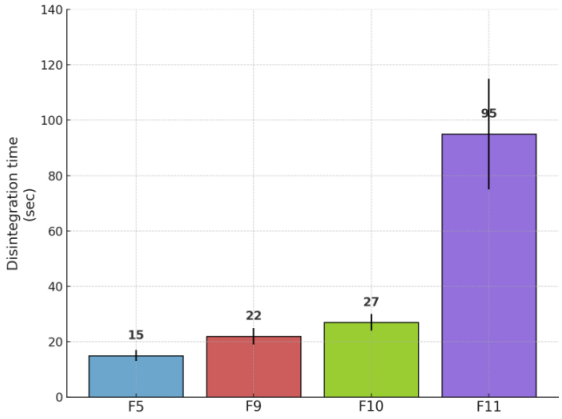

Figure 6. The disintegration time of the accepted formulas of meloxicam orally dispersible tablets

3.4.3. Content Uniformity and Weight Variation

The content of the tablets from the accepted formulas F5, and F11 was 93±0.5% and 90±1.2%, the weight variation was illustrated in Table 3. Content uniformity and weight variation for the tablets from the accepted formulas were within the required limit stated in European pharmacopoeia, as illustrated in **Table 3** (42).

Table 3. Quality control of the prepared meloxicam orally dispersible tablets.

Formulation Type	Disintegration time (sec.) (n=6)	Drug content(%) (n=10)	Hardness (Newton) (n=10)	Weight variation% (n=20)	Average Weight (g)	Thickness (mm) (n=10)	Diameter (mm) (n=10)
F5	14.6± 3.5	93±0.5	2.3±0.2	3.19±1.9	80.4±3	4.24±0.2	13
F9	21.6±3	-	1.56±0.55	5.8±2	20.5±5	2.2±0.07	13
F10	26.12±1	-	2.5±0.5	2.04±0.79	25±2.8	2.74±0.58	13
F11	96±20.8	90±1.2%	39.2 ±15.9	5.02±0.35	230 ±4.8	4.29±0.4	13

3.4.4. *In-vitro* dissolution test

The prepared MX ODTs F5 and F11 were subjected to *an in-vitro* dissolution study as shown in **Figure 7**, and **Table 4**. **Figure 8** illustrates the 2 minutes of drug release for both formulas; there was a statistical difference between them ($p<0.05$).

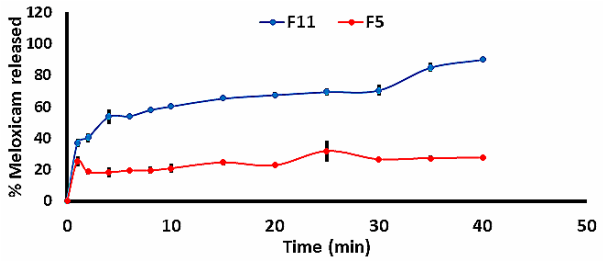

Figure 7. Percentage of meloxicam released from the lyophilized tablets of the formulas F5, and F11

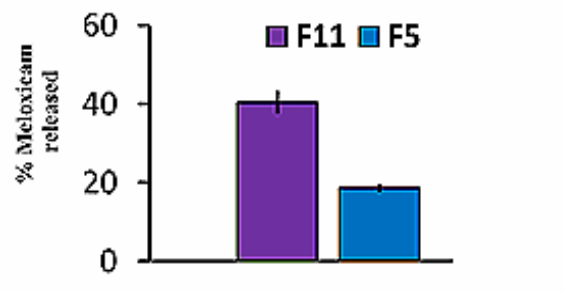

Figure 8. Comparison of a 2-minute meloxicam release from F11, and F5

The 2 minutes of drug release for F11 was 40.4±2.9%, while for F5 it was 18.6±1.9 %, there was a statistical difference between them ($p<0.05$), which indicated the effect of the hydrotropic agent (sodium benzoate 30%) on the solubility and the dissolution rate of MX, these results were correlated with the results obtained by Butt *et al.*, 2019, who formulated directly compressed tablets of rosuvastatin calcium with improved dissolution rate and extent of drug release due to the hydrotropic and micellar solubilization (43). There was an approximately complete release of the drug after 40 min in phosphate buffer (pH 6.8). On the other hand, in the formula F5, although the tablets had a rapid disintegration of (14.6± 3.5 sec), the amount of the drug released was only 18.6±1.9 % after 2 min with low, slow, irregular, and incomplete release of the drug during the stated period and medium as shown in table 4, Figure 7 and 8.

Table 4. The percentage of meloxicam released after 2 minutes from the lyophilized tablets of the formulas F11 and F5 (Mean±SD)

Formula type	% Meloxicam release after 2 minutes (n=6)
F11	40.4±2.9
F5	18.6±1.9

4. CONCLUSION

This study demonstrated a successful and straightforward combination technique to formulate MX ODTs with improved solubility as well as rapid disintegration and dissolution. The type and concentration of the excipient used played an important role in the rapidity of disintegration and release enhancement. In this study, different concentrations of hydrotropic agents (sodium acetate, sodium benzoate, urea) were prepared. The best solubility enhancement of MX was found by using a 30% concentration of sodium benzoate which was taken to formulate the F11 formula of ODTs. The F5 formula which contained (HPMC-E15 3% and poloxamer-188 1%) with no hydrotropic agent showed more rapid disintegration (14 sec) than F11. While the latter showed a better release profile than F5. It was concluded that there was complete compatibility of the tried hydrotropic agent and other excipients with MX and F11 was a promising ODT formula which combines both lyophilization and hydrotropic techniques to enhance the solubility and dissolution rate of the drug, however; the disintegration time of this formula still needs improvement. So, it was suggested for future studies to add a super disintegrant to F11 to improve disintegration. In addition to that, using a suitable method to mask the undesired taste of MX in the prepared tablets.

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تقييم أنظمة التجفيف بالتجميد الهيدروتروبي لتعزيز ذوبان الميلوكسيكام

الخلفية: إن انخفاض ذوبانية الميلوكسيكام (MX)يتطلب تطبيق استراتيجيات ما قبل الصياغة مثل الهايدروتروبية لتعزيز ذوبانيته وسرعة انحلاله. تمثل الأقراص الفوّارة عن طريق الفم (ODTs) خيارًا بديلًا للمرضى الذين يعانون من صعوبة في البلع، مما يُحسّن الامتثال للعلاج ويتجاوز تأثير المرور الأول. تهدف العديد من تقنيات تصنيع الأقراص الفوّارة، بما في ذلك التجميد بالتجفيف (Lyophilization)، إلى تحسين الأداء العلاجي للميلوكسيكام. **الطرق:** تم تحضير خمس مخاليط فيزيائية بنسب مختلفة من الميلوكسيكام إلى المضافات التالية: (HPMC-E15، الجلايسين، بنزوات الصوديوم، بولوكسامر-188، والمانيتول). كما تم إجراء تحليل مقارن للذوبانية باستخدام تراكيز مختلفة من عوامل الهايدروتروبية (بنزوات الصوديوم، أسيتات الصوديوم، واليوريا). تم تحضير الأقراص الفوّارة من الميلوكسيكام بالتجميد باستخدام المانيتول كمادة تشكيل والمادة الواقية الجلايسين. تم اختيار التركيبة المثالية وتعزيزها بعامل هايدروتروبي لتحسين ذوبانية الميلوكسيكام. ثم تم تقييم الأقراص من حيث الخصائص الفيزيائية، والانحلال، وسرعة التفكك، وتجانس محتوى الدواء للتأكد من مطابقتها للمواصفات الدوائية، بالإضافة إلى إجراء اختبارات FTIR وDSC على التركيبة المختارة. **النتائج:** أظهر تحليل الذوبانية أن بنزوات الصوديوم بتركيز 30% يُعد عاملًا هايدروتروبيًا فعالًا في إذابة الميلوكسيكام، مما ساعد في تكوين الأقراص المجففة بالتجميد. بعد عدة تجارب شملت دمج HPMC-E15، كاربومر-934، بولوكسامر-188، والمانيتول كمواد مالئة، أظهرت ثلاث تركيبات (F5، F9، F10) خصائص مقبولة بعد التجميد. من بينها، قدمت التركيبة F5 (HPMC-E15 3%، و1% بولوكسامر-188) أفضل أداء، وتم تعديلها لاحقًا إلى F11 بإضافة 30% بنزوات الصوديوم لتقييم تأثيرها على انحلال الميلوكسيكام. أظهرت نتائج تحليل التباين أحادي الاتجاه (ANOVA) لمعدل إطلاق الدواء خلال دقيقتين تحسنًا ملحوظًا، حيث حققت F11 نسبة إطلاق 40.4±2.9% مقارنة بـ 18.6±1.9% للتركيبةF5. **الاستنتاج:** أظهرت التركيبة F11 معدل انحلال محسّنًا، مما يشير إلى التأثير الإيجابي لبنزوات الصوديوم كعامل هايدروتروبي على ذوبانية الميلوكسيكام.