Effect of milling time on the release of Meloxicam-HPMC milled mixture

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Abstract
In this piece of work we investigated the effect of milling time on the release of meloxicam from the meloxicam-HPMC mixture. Meloxicam, a well-known non-steroidal anti-inflammatory drug, is poorly water-soluble drug which affects its bioavailability. For this reason many studies were performed to ensure its solubility. Milling of the pharmaceutical active ingredient nowadays pays researchers attention in order enhance the drug solubility via reduction particles size and/or through amorphisation. Recently, milling of the drug is consider as a green area for the production of amorphous solid dispersion due to the avoidance of solvent usage and heat. Polymers which are water soluble such as HPMC were used in the production of amorphous material due to its stabilisation and solubilisation effect.

In this work different milling time 10, 20, 30, 40 and 60 minutes were chosen for meloxicam-HPMC mixture. Then the dissolution study was performed using phosphate buffer at pH 7.4 for 120 minutes dissolution time. The effect of HPMC on the release was studied. Our results showed that the % of the drug release from meloxicam-HPMC mixture increased with increasing milling time. Furthermore, the release of meloxicam in the presence of polymer was higher than release of the drug alone. This could be attributed to the reduction in the particle size or due to the appearance of amorphous form after milling which increased with increasing milling time. Polymer enhances drug release by its solubilising and stabilising effect. This pre-formulation study is important for pharmaceutical industry to formulate this drug with easy and low cost method of preparation.

Keyword: Milling, release and meloxicam.

INTRODUCTION
For achievement of pharmacological activity, the active pharmaceutical ingredient must be soluble in the GIT fluid to enhance the drug bioavailability (1-3). Oral dosage form is the most common rout of administration due to the patient compliance, low cost, easily handling and stability (4). When the drug is given orally, it may be faced many hurdle such as dissolution, first pass effect, permeation through GIT membrane and so on (5, 6). Increasing numbers of poorly water-soluble drug and
increasing a challenge for their formulation results in raising attention for these drugs to solve these problems (7-9).

Active Pharmaceutical ingredients (APIs) are classified by Amidon et al. (1995) into four groups according to solubility and permeability known as the Biopharmaceutical Classification System (BCS) (10). Solubility is intrinsic property that can be modified by chemical modification of the drug such as salt complex or prodrug by solvent. On the other hand, dissolution is an extrinsic property that affected by physical, chemical and crystal engineering such as complexion, particle size reduction, surface modification, solid state transformation (11). These includes pH adjustment, self-emulsification, nano-suspension, co-solvency, micellar solubilisation, solid dispersions, cocrystals, and nanocrystallization. Selection of the best method depends on the physical property, carrier property and their uses (1, 5, 12). The first strategy is particles size reduction in which the rate of dissolution of a drug is affected by factors embodied in the Nooyse-Whitney equation (1, 13, 14). The bioavailability of a drug is thus dependent not just on its dissolution and solubility characteristics, but also on its membrane permeability and associated absorption related degradation, wider commercial and industrial applications than the "bottom-up" approach (e.g. precipitation) where fine particles are constructed from their dissolved molecular state and suitable solvents/anti-solvents of the drug need to be selected (15, 16).

Milling is used commonly for particles size reduction using cutter mill, roller mills, pestle and mortars and runner mills (17). For example Griseofulvin, an antifungal drug is an example of drug where solubility and dissolution is enhanced by milling. Other example is carbamazepine where milling enhance drug dissolution (15). Prodrug is an example of increasing solubility for both class II and class VI drugs by which chemical modification of the drug (18). Once the parent drug is absorbed, the prodrug is rapidly cleaved by an enzyme to release the parent drug. Example for this type is acyclovir, enalapril and gabapentin (19, 20). Other method to enhance drug solubility is complexion by using cyclodextrins (CD) which is cyclic oligomers that composed of 6–8 glucose units which have the ability to form non-covalent, dynamic complexes with lipophilic molecules by inclusion. On dilution, the drug will be released rapidly for example proteins and peptides (1, 21). Salts formation is other method for enhancing drug solubility. The pH profile is important for selection of the best molecules. Buffer salts as well as hydrates might have different solubility characteristics (1, 22). Lipid base formulation is another important strategy for improvement of poorly water-soluble drug mainly lipophilic drugs. By this method lipid can alter both physicochemical property of the drug and absorption pathway (23). The secretion of lipases and co-lipases from the salivary gland results in lipid digestion into triglyceride and into mono and di glyceride and fatty acid (24). Amorphous solid dispersion is an important method for enhancing the solubility of poorly water soluble drug (25, 26). In 1970s Chiou and Riegelman defined it as a dispersion of an API in an inert carrier in the solid state prepared by solvent, melting or solvent-melting methods (27). Nowadays, the term solid dispersion is mostly linked to glass solutions of poorly soluble compounds with amorphous carriers in which both API and other molecules are intimately mixed with the carrier (28).

Stabilisation of the amorphous form in the solid dispersion depends on many factors such as intermolecular forces, anti-plasticising effect of the polymer and the glass transition temperature of the mixture (29). Polymer both stabilise and solubilise the solid dispersion mixture. In addition, it plays an important role in improving supersaturation of the drug inside the GIT (30-32). Crystalisation is the major problem in amorphous solid dispersion (26,27,33). Crystalisation affected by high temperature, humidity and mechanical stress (31, 34, 35). Mechanical activation such as milling can results in amorphous forms (36). Other method involve dissolving in a solvent or melt the crystal form to break the crystal lattice structure. The cooling of the API from the molten state (Hot melt extrusion (HME)) or rapid solvent evaporation (Spray drying) from the dissolved state leads to amorphous forms (31).

Meloxicam (MEL) is a non-steroidal anti-inflammatory drug (NSAID) used to treat rheumatoid arthritis, osteoarthritis, and postoperative pain. Meloxicam molecular weight 351, log P 2.2 and pKa 3.9 (37). This drug is poorly water soluble, for this reason improving water solubility is important for this drug (38).

### MATERIALS AND METHODS

#### Materials

Meloxicam was kindly donated form Al-Furat factory, Baghdad-Iraq, HPMC Prowizer pharma India, sodium lauryl sulphate (SLS) form Fluka chemical. Buchs, sodium dihydrogen orthophosphate dihydrate, di-sodium hydrogen orthophosphate dihydrate form Thomas Baker, India.

#### Preparation of buffer solution

Buffer solutions were prepared according to united state Pharmacopoeia monographs. Phosphate buffer 7.4 was prepared by dissolving sodium dihydrogen orthophosphate dihydrate, di-sodium hydrogen orthophosphate dihydrate in sufficient water to produce 1000 ml with one-hour sonication using SB-25-12 DTDN ultrasonic cleaner, China. The pH of the mixture was performed using Ohaus Inolab, China.

#### Calibration curve

Calibration curve was made form serial dilution of meloxicam in phosphate buffer 7.4 the concentration was read using UV spectroscopic method using Shimadzo 1650 pc, Japan. In this method, 20 μg/mL solution of meloxicam was prepared by appropriate dilution of standard stock solution and scanned in the spectrum mode from 400 nm to 200 nm.

#### Milling of the content

Meloxicam was milled for 10 minutes alone. Then about 25% drug was milled with 75% of HPMC for 10, 20, 30, 40 and 60 minutes by using mortar and pestle.

#### Dissolution study

Dissolution experiments were Cosmolab dissolution apparatus, India. Type II at 37° at a paddle speed of 100 rpm. The dissolution medium was 900 ml of either water or a mixer of water and SLS solution, selected on the basis of solubility data obtained from the experiments using 0.2% of SLS in water. These mediums were also used to test the dissolution of bulk powder (100 mg, particle >200 μM) of meloxicam. 5 mL samples were withdrawn at periodical interval and analysed.

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spectrophotometrically at 363 nm. The same volume of dissolution medium maintained at 37° was added to maintain constant volume and sink condition.

III RESULTS AND DISCUSSION

Calibration curve

Figure 3.1 shows the calibration curve for meloxicam in phosphate buffer with pH 7.4. The spectra showed sharp peak at 363 nm. The calibration curve for Meloxicam was plotted in the concentration range of 1–7 μg/mL at wavelength 363 nm. A linear relationship was obtained. This equation will be used in the calculation of the % of the drug release in the dissolution study which will be shown below.

![Figure 3.1- Calibration curve of meloxicam in phosphate buffer 7.4](image)

Effect of milling on the release of meloxicam

Figure 3.2 that shows the release of meloxicam and milled meloxicam in the dissolution media. It is clearly seen that the release of the as received meloxicam in phosphate buffer is about 6% while after milling the percentage of drug release increased form 6% to about 12%. The effect of milling on the increasing of the release rate of the drug can be seen after milling of indomethacin (39, 40). The increasing in % of the drug release can be attributed to the reduction in the particle size according to Noys-Whitny equation. In addition the reduction in the particle size, the % of the drug release can be result from the changing the crystal habit after milling due to the reduction in the crystallinity of the drug and increasing in the amorphous content (39, 41).

![Figure 3.2- Release of meloxicam, as received and milled for 10 minutes in phosphate buffer for 120 minutes](image)

Effect of HPMC addition on the release of meloxicam

Figure 3.3 shows the release of meloxicam as received and meloxicam–HPMC in phosphate buffer at pH 7.4. It is clearly seen form this figure that the release rate of meloxicam after addition of HPMC increased form 6% to about 16%. Such effect was seen in increasing the release of carbamazepine was increased with addition of HPMC (42). The effect of addition of HPMC on the increasing the release of the poorly water soluble drug can be attributed to the formation of H-bond between the drug and HPMC which results in increasing its solubility (43, 44). HPMC can acts also acts surface active agent that enhance its water solubility.
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Figure 3.3– Release of meloxicam, as received and meloxicam-HPMC in phosphate buffer 7.4 for 120 minutes

Figure 3.4– Release of meloxicam, as received and milled for 10, 20, 30, 40 and 60 minutes in phosphate buffer at pH 7.4 for 120 minutes

Effect of milling time on the release of meloxicam-HPMC

Figure 3.4 shows the release of milled meloxicam-HPMC mixture on different time of milling 10, 20, 30, 40 and 60 minutes. Its clearly seen form the figure the % of the drug release increased with increasing milling time. The same results was seen after milling of vitamin E, as increasing milling time the % of the drug release was increased (45, 46). The interpretation of this might be related to reduction of the particle size which further increasing the release rate. In addition, this might be related to increasing the amorphous content which leads to increasing the solubility of the drug that is protected by the addition of polymer and enhancing the dissolution of it.

CONCLUSION

From our data it can be concluded that milling the drug with a water-soluble polymer can result in enhancing the drug release for its mixture prior to the formulation step. Increasing milling time results in more enhancing in the percentage of drug release which might be result from increasing the surface area of the drug particles and /or increasing in the amorphous content of the mixture. This will results in increasing the bioavailability of meloxicam which is the target of the pharmaceutical field.

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