Research Article

Formulation and *In -vitro* Evaluation of Fast Dissolving Tablets of Meloxicam Solid Dispersion

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ABSTRACT

This study concerned with preparation and in-vitro evaluation of fast dissolving tablets of meloxicam solid dispersion, since meloxicam is a practically insoluble in aqueous media after oral administration and the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by incorporating the drug in a fast dissolving dosage form as a solid dispersion that prepared using polyethylene glycol (PEG6000) in different ratios and different methods of preparation including melting, solvent evaporation, and grinding and microwave fusion methods. The fast dissolving tablets were prepared using sodium starch glycolate (SSG) and croscarmellose sodium (CCS) in different concentration as superdisintegrants and using mannitol and avecil as diluent. The prepared solid dispersion was evaluated for in vitro release profile. The prepared tablets were evaluated for thickness, hardness, friability, disintegration time and in vitro dissolution. Among the prepared formulation of solid dispersion, F2 which prepared by melting method using 1:3 drug: polymer ratio showed 100% of drug release at the end of 10 minutes and found to be promising. Fast dissolving tablets of F8, which prepared from meloxicam solid dispersion of F2, 4% CCS and mannitol as diluent showed 100% of drug release at the end of 10 minutes and the results for the other tests were satisfactory. F8 was selected as optimum formula with improving solubility of the drug resulting in increasing bioavailability after oral administration.

Keywords: Meloxicam, Solid dispersion, Fast dissolving tablet, Melting method, Fusion method, PEG 6000, CCS, Mannitol.

INTRODUCTION

Tablets offer advantages over both patients and manufacturers due to their simplicity and economy of manufacture, relative stability and convenience in packaging, shipping and storage. For the patients, convenience in administration, accurate dosing and stability compared to oral liquid, tamper-proofness compared to capsule, safe compared to parental dosage forms [1]. However, some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms [2]. Other groups include mentally ill and the developmentally disabled. In some cases such as motion sickness, sudden episodes of allergic attack or coughing and unavailability of drinking water, swallowing of conventional tablets is difficult [3]. Recent advances in novel drug delivery system (NDDS) aim to enhance safety and toxicity of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach led to development of fast dissolving tablets [4]. Fast dissolving/disintegrating tablets (FDDTs) are solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue [5]. The tablets disintegrate into smaller granules or melt in the mouth from a hard solid structure to a gel like structure, allowing easy swallowing by the patients [6].

Meloxicam is a non-steroidal anti- inflammatory drug (NSAID) belonging to the class of oxicams. In addition to its analgesic and antipyretic effect it is widely used in the treatment of rheumatoid arthritis, ankylosing spondulytis and osteoarthritis. It is also indicated for the management of dental pain, post-traumatic and post-operative pain, inflammation and swelling. Recently, meloxicam has been considered as a potential drug for the prevention and treatment of colorectal polyps [7].

Meloxicam chemical formula is ($C_{14}H_{13}N_3O_4S_2$), it is practically insoluble in water. This low solubility in biological fluids, results into poor bioavailability after oral administration [8]. Poor water soluble drugs are allied to slower rate of absorption from oral route, so, there is a necessity to enhance the dissolution of these drugs to ensure maximum therapeutic utility of these drugs [9].

For enhancement of solubility and dissolution rate of poorly soluble drugs , abundant commercially viable methods are available . Solid dispersion is the mainly promising method to formulators because of its simplicity of preparation, ease of optimization, and reproducibility [10].

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [11].

Hence, in present study we attempted to improve the dissolution of meloxicam through the formulation of tablets containing solid dispersion prepared by melting , solvent evaporation, grinding and microwave methods using PEG6000 as carrier, CCS and SSG as superdisintegrant.

MATERIALS AND METHODS

Material

Meloxicam was obtained from Ajanta, India, PEG 6000 from Sigma (UK), CCS, SSG, magnesium stearate, avecil and sodium saccharin from Samara Drug Industry (SDI), Iraq. Potassium hydrogen orthophosphate (KHPO4) from GCC analytical reagent, chloroform from BDH chemicals Ltd, UK, methanol and Potassium hydroxide (KOH) from SDI, Iraq.

Preparation of Solid Dispersion

Meloxicam solid dispersions were prepared by using four different method, melting, fusion, microwave and solvent evaporation method and using PEG6000 as hydrophilic carrier as shown in table 1.

Melting method

Solid dispersion of meloxicam in PEG6000 containing two different ratios (1:2 and 1:3 w/w) respectively were prepared by melting method . Amount of drug and polymer were mixed in glass vial, the mixture was then heated using water bath at 70°C until it was completely melted, continuous stirring during the melting was carried out to prevent the separation of the constituents . The melt was rapidly solidified , the solidified mass was then crushed, size reduced in mortar and pestle and sieved through 0.63 mm sieve[12].

Solvent evaporation method

Solid dispersion of meloxicam in PEG6000 containing ratio (1:3) was prepared by solvent evaporation method. Meloxicam and PEG6000 were dissolved in 50 ml of chloroform. The solvent was stirred by stirrer and left to evaporate at room temperature 25°C. The solidified mass was then crushed, size reduced in mortar and pestle and sieved through 0.63 mm sieve[13].

Grinding method

Solid dispersion of meloxicam in PEG6000 containing ratio (1:3) was prepared by grinding method. Drug and PEG6000 are mixed together with one mL of water. The damp mass was obtained and then crushed, size reduced in mortar and pestle and sieved through 0.63 mm sieve [14].

Microwave induced fusion method

Solid dispersion of meloxicam in PEG6000 containing ratio (1:3) was prepared by microwave induced fusion method. Meloxicam and PEG6000 was taken in a glass beaker. The beaker was subjected to microwave and heating for three minutes at the power of 1000 W . After three minutes beaker was removed from microwave and the product was cooled at room temperature 25°C. Product was sieved through 0.63 mm sieve [15].

Table 1: Different Formulas of Meloxicam Solid Dispersion

Formula code	Meloxicam (mg)	PEG6000 (mg)	Method
F_1	100	200	Melting
F_2	100	300	Melting
F_3	100	300	Solvent
F_4	100	300	Grinding
F_5	100	300	Microwave

In vitro release studies

The *in vitro* release study was performed for all the prepared solid dispersion formulas (F1, F2, F3, F4 and F5) by using USP-II paddle apparatus. In this 500 mL of phosphate buffer PH 6.8 was used and maintained temperature at 37°C with 50 rpm. Five mL of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium at a certain intervals for 30 minutes. The sample withdrawn was filtered and diluted with Phosphate buffer pH 6.8 prior to analysis in the UV spectrophotometer at 362 nm [16].

Preparation of fast dissolving tablets

Fast dissolving tablets of meloxicam solid dispersion were prepared by direct compression method according to the formulas given in table 2. Solid dispersion of F2 was selected to prepare the tablet since it gave the best release profile. All the ingredients were weighed and kept separately. Then the weighed ingredients were mixed in geometrical order with weigh meloxicam solid dispersion and blend together to get uniform mixture. Then tablets were compressed using 6mm sizes biconvex round punch and compression force equal to 7 ton to get tablet using tablet compression machine [17].

Table 2: Composition of Fast Dissolving Tablets

Ingredient (mg)	F6	F7	F8	F9	F10
Meloxicam SD	30	30	30	30	------
Meloxicam	--------	--------	--------	-------	7.5
Sodium starch glycolate	2	--------	---------	-------	------
Crosscarmelose Sodium	-------	2	4	4	4
Mg starate	1	1	1	1	1
Mannitol	67	67	65	-------	65
Avecil	--------	--------	--------	65	-------
Total weight	100	100	100	100	100

Evaluation of fast dissolving tablets

Weight variation

Twenty tablets were selected randomly, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 5% [18].

Tablet thickness

The thickness was measured by placing tablet between two arms of the Varnier calipers. Three tablets were taken and their thickness was measured [19].

Hardness

The resistance of tablets to shipping or breakage, under the conditions of storage, transportations and handling before usage depends on its hardness. Hardness was determined by taking three tablets from each formulation, using an electrical hardness tester[20].

Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately (W_1) and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed ($W_{2)}$ and the percentage loss was determined [21].

$$\text{Percentage Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Disintegration test

The disintegration test is performed using an USP disintegration apparatus with phosphate buffer PH 6.8 at 37°C. The time reported to obtain complete disintegration of three tablets are recorded and average is reported [22].

***In- vitro* release study**

The release of from formulated FDTs was determined using USP dissolution testing apparatus. The dissolution test was performed using 500 mL of phosphate buffer solution, pH 6.8 at 37 °C and 50 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at specific time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through filter paper. Absorbance of these solutions was measured at 362 nm using a UV Spectrophotometer. Cumulative percentage (%) of drug release was calculated using standard plot of meloxicam[23].

Statistical analysis

The results of the experiments were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

RESULTS AND DISSCUSSION

***In vitro* release study of solid dispersion**

In vitro release study of solid dispersion was performed in phosphate buffer pH 6.8 .The results showed that that drug exhibited slower release profile as compared to F2 (solid dispersion) which showed significant ($P < 0.05$) enhancement in dissolution rate where 43.6 % and 100 % of drug was released from the drug powder and solid dispersion in 10 min respectively as shown in figure 1. This is may be due to the fact that the amorphous form of a drug has a higher thermodynamic activity than its crystalline form, resulting in the rapid dissolution of the drug. It is usually believed that a drug in a solid dispersion system commonly exists in an amorphous form. Furthermore, the reduced particle size and accordingly elevated surface area could elevate the dissolution rate of meloxicam in the solid dispersions. In addition to the latter evidences, increasing drug wettability and solubility besides deaggregation of the drug particles caused by the polymers could be the reasons for enhanced drug release rate from the solid dispersions [24].

Increasing PEG6000 ratio in solid dispersion (F1,F2) cause significant increase in drug release ($p<0.05$) where 91.8 % and 100% of drug released from F1 and F2 in 10 min respectively as shown in figure 2. The dissolution profile of drug from solid dispersions was found to be dependent on drug – carrier ratio. As the proportion of the PEG6000 in solid dispersion increased , dissolution rate increased which may be is due to hydrophilicity of the carriers. Hydrophilic polymers caused aggregation reduction, wettability improvement and local solubilization in the diffusion layer and thereby increasing in the dissolution rate [25].

The effect of method of preparation of drug release was studied by comparing F2, F3, F4 and F5 which were prepared by melting, solvent evaporation, grinding, and microwave induced fusion method respectively. It was observed as shown in figure 3 that the release of drug increased when solid dispersion was prepared by melting method rather than by other methods. This is due to the fact that solid dispersion prepared by melting method result in a more uniform dispersion of the drug in the hydrophilic carrier matrix as compared to those prepared by other methods. This rapid release was attributed to very fine state of subdivision of the drug particles, and solubilizing plus wetting effect of the carrier[26].

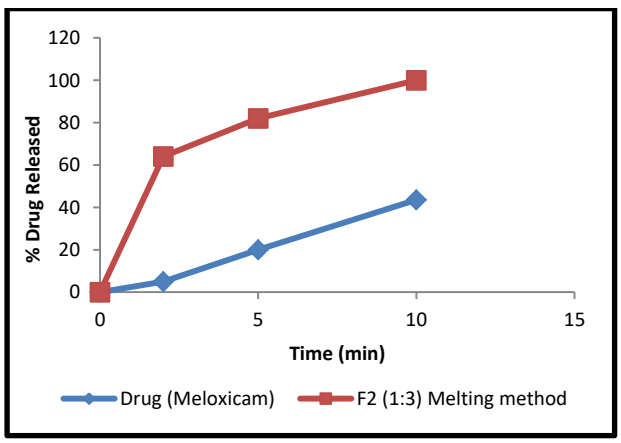

Figure 1: *In- vitro* release profile of drug and solid dispersion

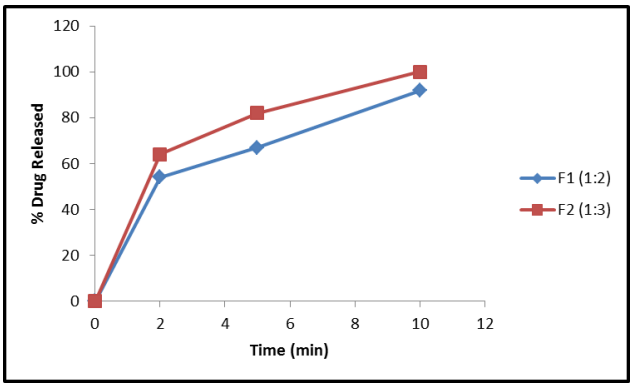

Figure 2: The effect of drug: polymer ratio on the release profile

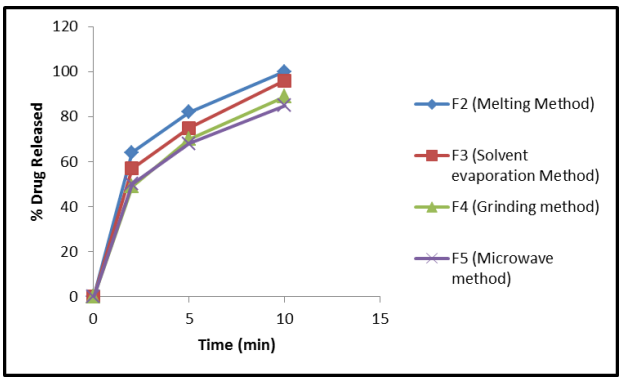

Figure 3: The effect of methods of solid dispersion preparation on the release profile

Evaluation of fast dissolving tablets

Tablets thickness, hardness, friability and disintegration time

From the results obtained it was seen that the average weights for all the prepared formulas were uniform and comply with referred values. The thickness was found to vary between (3.12 to 3.17 mm). These results show that all tablets possessed uniform thickness with minor differences with constant tablet weight indicating acceptable compressibility of all formulations. All the prepared tablets have hardness in range of 3.5 kg/cm^2 to 4 kg/cm^2 indicating that the tablets are of adequate strength property to resist handling and mechanical stress.

The composition must be selected in order to obtain final tablets with mechanical properties able to grant resistance to capping, abrasion or breakage under storage conditions, transport and handling before usage. Thus, this aspect was evaluated by subjecting tablets to friability test. The weight loss resulted is lower than 1% (0.2–0.9%) for all tablets indicating good compactness and mechanical resistance.

The most important parameter that needs to be optimized in the development of fast dispersible tablets is the disintegration time of tablets. In the present study, all the tablets disintegrated in ≤58 sec fulfilling the official requirements (<3 min) for dispersible tablets. It was observed that the disintegration time was decrease from (58 to 30 sec) ($p<0.05$) when the concentration of increased. This can be explained by the fact that although superdisintegrants may sorb liquid and cause swelling of the compact in proportion to the amount added, sufficient disintegrant must be present to expose primary particles upon disintegration. Too few disintegrant particles per unit volume of compact may only lead to the production of larger aggregates, which will have difficulty in further de-aggregation [27].

Table 3: The physicochemical parameters of fast dissolving tablet

Formula code	F6	F7	F8	F9	F10
Average weight (mg)	96	98.5	97	97	98.6
Thickness (mm)	3.15	3.16	3.16	3.17	3.12
Hardness (Kg/Cm^2)	4	3.5	4	3.5	4
Friability% (w/w)	0.9	0.5	0.4	0.2	0.9
Disintegration time (sec)	50	58	30	15	35

***In- vitro* release study of fast dissolving tablets**

In- vitro release study of fast dissolving tablets was performed in phosphate buffer pH 6.8. Increasing CCS concentration in the prepared tablets (F7,F8) results in significant increase in drug release ($p<0.05$) where 91.5% and 100% of drug released from F7 and F8 in 20 minutes respectively as seen in figure 4. This increase in meloxicam release is attributed to rapid swelling and disintegration of tablet into apparently primary particles[28].

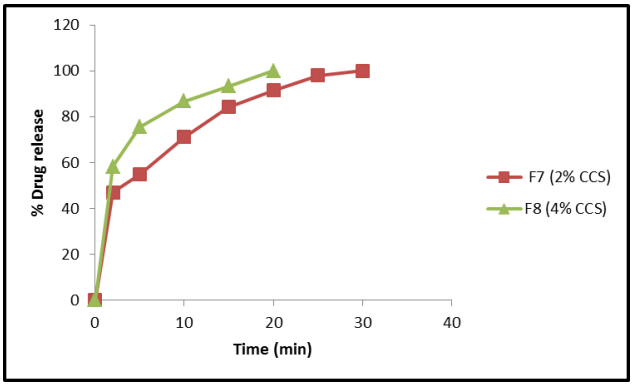

Figure 4: Effect of concentration of superdisintegrant on drug release

Formulas containing CCS as superdisintegrant (F7) showed significant increase in drug release ($p<0.05$) than that from tablets containing SSG (F8), where 75% and 100% of drug released from F6 and F7 in 30 min respectively as shown in figure 5. The increased dissolution of meloxicam with CCS may be due to rapid swelling and disintegrating tablets rapidly into apparently primary particles. While tablets formulated with SSG, disintegrate by rapid uptake of water, followed by rapid and enormous swelling into primary particle but more

slowly due to the formation of a viscous gel layer by SSG[29].

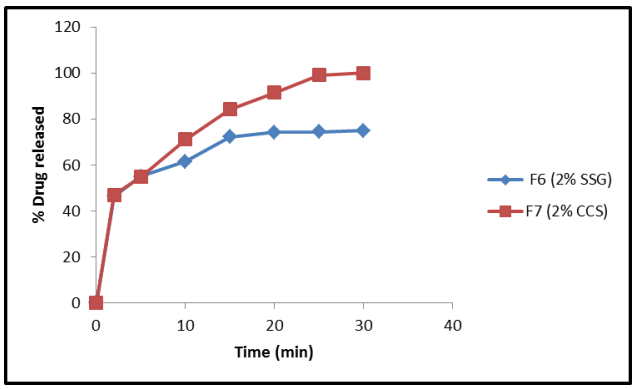

Figure 5: Effect of type of superdisisintigrant on drug release

Drug powder was used (F10) instead of meloxicam solid dispersion (F8) to study the effect of solid dispersion on the release of meloxicam from fast dissolving tablets. The results as shown in figure 6 indicate that the rate of drug release increased significantly($p<0.05$) when drug used as solid dispersion as in F8 compared to F10 where 100% and 68% of drug released in 25 min respectively. This can be attributed to the presence of drug in amorphous form, increased wettability and dispersibility and particle size reduction [30].

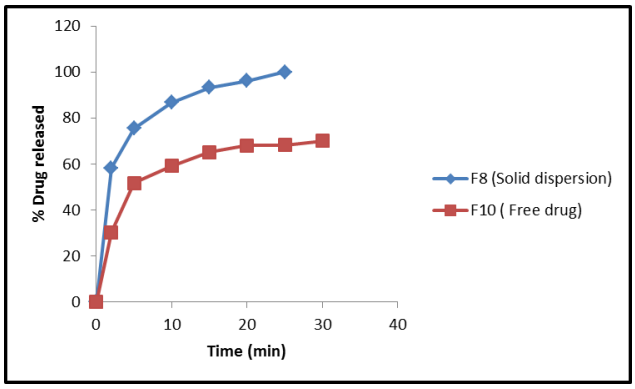

Figure 6: Effect of type of solid dispersion on drug release

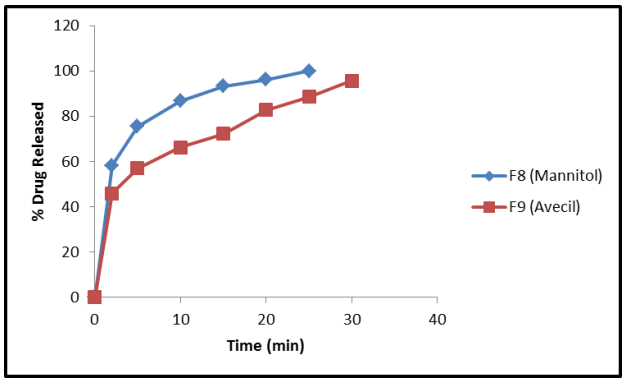

Figure 7: Effect of type of diluents on drug release

Mannitol in F8 was replaced by avicel (F9) to study the effect of diluent's type on drug release from fast dissolving tablets. As shown in figure 7, F8 which contains mannitol as diluent showed non-significant ($p>0.05$) increased in drug release comparing to F9 which contains avacil as diluent were 100% and 96% of drug released in 25 min respectively. This is related to the low solubility of avicel in water as compared to mannitol. High solubility of mannitol led to pores formation in the matrix which allows the penetration of the dissolution medium into the matrix [31].

CONCLUSION

In the present study meloxicam solid dispersion was prepared by different methods using PEG6000 as a hydrophilic carrier in different ratios. The meloxicam solid dispersion prepared by melting method using PEG6000 as a hydrophilic carrier in a ratio of 1:3 can be successfully used to improve its dissolution as indicated by *in vitro* dissolution studies. This solid dispersion was further formulated as FDTs using SSG and CCS as superdisintegrants, mannitol and avicel as diluents in order to gain better patient compliance and effective therapy. Tablets thickness, hardness, friability, disintegration time and *in vitro* release studies were performed for the prepared tablets. Formulation containing 4% (w/w) CCS and mannitol as diluent was considered as the best formulation as it give best drug profile in addition to a satisfactory results for other tests.

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