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Formulation and Optimization of Fast Dissolving Tablets of Meloxiam by Lyophilisation Mehod

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ABSTRACT

Lyophilisation is the most successful novel method for manufacturing of fast dissolving tablets (FDTs). In present study FDTs of meloxicam were prepared using lyophilisation method. Meloxicam is an anti-inflammatory drug used in rheumatoid arthritis. It is poorly soluble drug so efforts were made to increase its dissolution by incorporating SLS in formula. Physical properties of the tablets were optimised taking various concentrations of ingredients like gelatine as matrix forming agent, glycine and mannitol as bulking and elegance imparting agent and sodium alginate as viscosity increasing agent. SLS (0.3%w/v) was proved efficient in increasing dissolution of meloxicam. Tween20 and tween80 were used to decrease the disintegration time of the FDTs.

Keywords: Lyophilisation, meloxicam, gelatine, lyophilised tablet index (LTI), sodium alginate, SLS.

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INTRODUCTION

The oral route of drug administration is most common and convenient method for patient use since time. However, many patients have dysphagia or difficulty in swallowing tablets and hard gelatine capsules and therefore they do not take medication as prescribed by physicians [1,2]. New drug delivery systems like fast dissolving or orodispersible tablets that dissolve or disperse quickly in a few seconds after placement in the mouth without water can alleviate the problem of swallowing tablets [3]. Meloxicam is a non steroidal anti-inflammatory drug prescribed for osteoarthritis and rheumatoid arthritis the diseases most prevalent in the geriatric patients. The preparations of anti-inflammatory drugs are meant to produce therapeutic effect immediately after their administration as inflammation is mostly an acute condition needed to be cured symptomatically as first line of treatment. Unfortunately meloxicam is poorly soluble drug having higher time of onset of action. As it falls under BCS class –II drugs its effect is dissolution rate limited. By improving the dissolution of meloxicam its time of onset of action can be reduced. The administration of meloxicam as fast dissolving formulation with improved dissolution may improve patient compliance by ease of taking medicine without need of water and with the will of actually taking medicine. It may improve the therapeutic effectiveness of drug by dissolving in saliva and thereby quick onset of action with bypassing the first pass metabolism.

Freeze drying process (lyophilization) for manufacturing FDTs has been the most successful commercial FDT technique. This process has been used to manufacture commercial FDTs for many drugs. Manufacturing of FDTs by this process involves the removal of water by sublimation from the liquid mixture of drug, matrix former and other excipients filled into preformed blister pockets. In this study FDTs of meloxicam were made using various ingredients [4-9].

MATERIALS AND METHODS

Materials

Meloxicam was obtained from Acme pharmaceuticals ltd., Ahmedabad as a gift sample. gelatine, Glycine and sodium alginate were obtained from SD Fine chemicals, Mumbai. Sodium lauryl sulphate (SLS), mannitol, citric acid, Tween 20 and Tween 80 were obtained from Finar reagent, Ahmedabad. Aspartame was obtained from Himedia labs, Mumbai.

Methods

Preparation of the tablets

Preparation of the solution

Gelatine was first dissolved in distilled water at about 40^{o}C to obtain the required concentration. Mannitol and glycine were then added to the gelatine solution in the

predetermined concentration. The solution was stirred on stirrer till they get completely dissolved. Then required quantity of aspartame and citric acid was added and stirred till they get dissolved. Then sodium alginate is added in the solution and stirred till it get completely swell and dissolve leaving the solution clear and free of air bubbles. Then measured quantity of SLS and T80 or T20 is added in the solution while stirring. To this solution, an accurately weighed quantity of meloxicam is added. The quantity of meloxicam in the solution was adjusted such that final solution contained 15 mg of meloxicam per 0.5 ml of solution. The sequence of addition of ingredients while preparing the solution was adjusted according to the formula.

Lyophilisation of the tablets

Accurately measured quantity of 0.5 ml of solution is filled in each cavity of PVC blisters having concave shape with size of 1.8mm diameter and 0.5 mm depth. The filled blisters are then transferred to deep freezer and kept at -20^{o}C for 24 hrs. The frozen blisters are then transferred to lyophilizer (Virtis Benchtop K series lyophilizer) for 24 hrs at condenser temperature -100^{o}C and pressure of 35 mTorr. At the end of process the tablets were separated out of the blisters and allowed for further evaluation. The prepared tablets were stored in desiccator using $CaCl_2$ as desiccant at 0% relative humidity and cool temperature. [2]

Optimization of lyophilised tablets

Optimization of the tablets was done on step by step basis. First, concentration of gelatine was optimised making tablets of only gelatine having different concentrations (Table 1). Then concentrations of Glycine and mannitol were optimised taking different concentrations (Table 2). In this step the formula was included with the concentration of gelatine which was selected from results of previous step. The optimised formula from this step was selected for further optimization of viscosity increasing agent (Sodium alginate). Batches were prepared taking different concentrations of sodium alginate in the optimised formula of the previous step (Table 3). Then concentration of solubilizer (SLS) was optimised by including different concentration of it in optimised formula of previous step (Table 4). Concentration of disintegration enhancer (Tweens) was optimised taking basis of the previous step of optimised solubilizer (Table 5).

Table 1: Batches for selection of gelatine concentration

Ingredient	Batch code			
Gelatine (con. in solution as %w/v)	G1	G2	G3	G4
	0.5	1.0	1.5	2.0

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Table 2: Batches for selection of concentration of glycine and mannitol

Ingredient	Batch code					
	E1	E2	E3	E4	E5	E6
Gelatine (%w/v)	1.5	1.5	1.5	1.5	1.5	1.5
Glycine (%w/v)	0.5	1.0	1.5	2.0	2.5	3.0
Mannitol (%w/v)	0.5	1.0	1.5	2.0	2.5	3.0

Table 3: Batches for selection of concentration of sodium alginate

Ingredient	Batch		
	N1	N2	N3
Gelatine (%w/v)	1.5	1.5	1.5
Mannitol (%w/v)	2	2	2
Glycine (%w/v)	2	2	2
Meloxicam (%w/v)	3	3	3
Sodium alginate (%w/v)	0.5	1.0	1.5
Aspartame (%w/v)	1	1	1
Citric acid (%w/v)	1	1	1

Table 4: Batches for selection of concentration of SLS

Ingredient	Batch		
	R1	R2	R3
Gelatine (%w/v)	1.5	1.5	1.5
Mannitol (%w/v)	2	2	2
Glycine (%w/v)	2	2	2
SLS (%w/v)	0.1	0.2	0.3
Meloxicam (%w/v)	3	3	3
Sodium alginate (%w/v)	0.5	0.5	0.5
Aspartame (%w/v)	1	1	1
Citric acid (%w/v)	1	1	1

Table 5: Batches for selection of concentration of tweens (Disintegration enhancer)

Ingredient	Batch			
	T1	T2	T3	T4
Gelatine (%w/v)	1.5	1.5	1.5	1.5
Mannitol (%w/v)	2	2	2	2
Glycine (%w/v)	2	2	2	2
SLS (%w/v)	0.3	0.3	0.3	0.3
Meloxicam (%w/v)	3	3	3	3
Sodium alginate (%w/v)	0.5	0.5	0.5	0.5
Aspartame (%w/v)	1	1	1	1
Citric acid (%w/v)	1	1	1	1
Tween 20 (%w/v)	0.1	0.2	-	-
Tween 80 (%w/v)	-	-	0.1	0.2

Evaluation of the prepared tablets

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Weight Variation

The weights were determined by using Sartorious balance (Model CP- 224 S). Weight control is based on a sample of 20 tablets. Determinations were made in triplicate.

Tablet hardness

Tablet hardness was measured using digital hardness tester. The hardness was expressed in newtons (N).

Tablet friability

The friability of a sample of 20 orally disintegrating tablets was measured utilizing a USP-type Roche friabilator (Camp-bell Electronics, Mumbai). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed and percentage weight loss (friability) was calculated.

In vitro disintegration time

Disintegration times of the prepared ODTs were determined in distilled water kept at 37 ± 0.5^{o}C using a DST- 3 disintegration tester (Logan Instruments Corp., NJ, USA). The disintegration time was defined as the time necessary for the FDT to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. A digital stopwatch was used to measure the disintegration time to the nearest second. Only one ODT was analyzed at a time in order to ensure utmost accuracy.

Wetting Time

A piece of filter paper was saturated with water and put on a flat surface. A tablet was carefully placed on the surface of the filter paper. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. Wetting time was recorded using a stopwatch.

Moisture analysis

The tablets were analysed for their residual moisture content after lyophilization using Karl Fischer titration (Veego Matic-MD, Veego Instruments Corporation, India). The instrument was calibrated using sodium thiosulphate pentahydrate and methanol as a standard. Each tablet was pulverized, inserted in the titration vessel and analysed after a stirring time of 3 min.
Factor: 1ml of Karl Fischer reagent ≈ 4.02 mg of H_2O

Assay

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Orally disintegrating tablet formulations were assayed for drug content. 10 tablets were randomly selected from each formulation and pulverized to a fine powder. Weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate and assayed for the drug content utilizing a UV spectrophotometer (Shimadzu UV-1601 UV/Vis double beam spectrophotometer).

Scanning electron microscopic (SEM) analysis

Surface morphology and cross-sections of selected tablet formulations were examined using Jeol JSM-6400 scanning electron microscope (Tokyo, Japan). Cross-section samples were prepared by cutting a thin slice of the tablet using a scalpel.

RESULT AND DISCUSSION

Preformulation

FTIR spectrum of meloxicam showed distinct peaks at 3291 cm^{-1}, 1620 cm^{-1} (-NH), 1580 cm^{-1} (CO) (Figure 1). These peaks can be seen in the spectra of formulation mixture of meloxicam and other excipients. It indicates that the structural characteristics of meloxicam are retained in the mixtures (Figure 2). So there is no interaction between meloxicam and formulation excipients.

The mean particle diameter was found to be 45 µm. More than 50% of particles were found to be within the range of 35µm - 45µm which shows precise particles size distribution (Figure 3) and (Figure 4). It indicates that obtained meloxicam powder can be used for preparation of dispersion without any apparent settling problem.

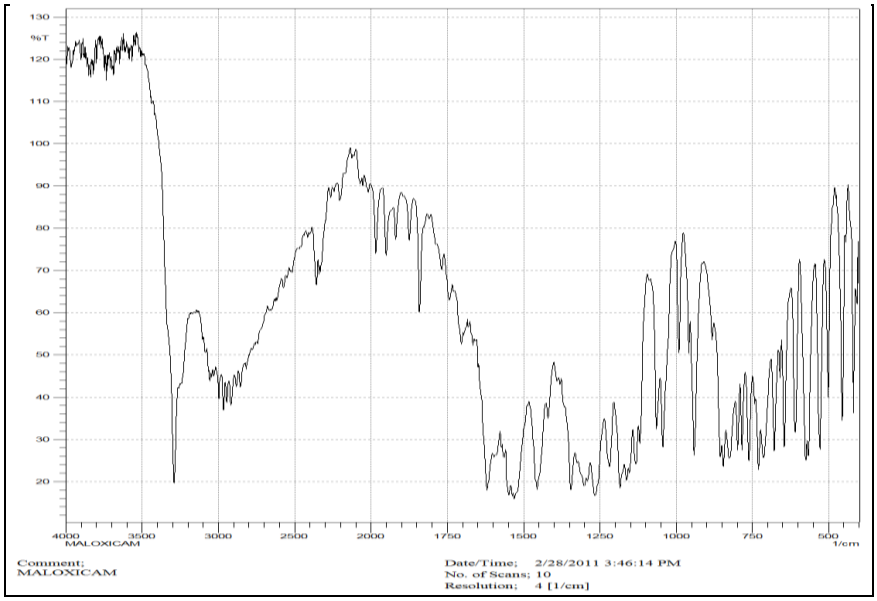

Figure 1: FTIR spectrum of meloxicam

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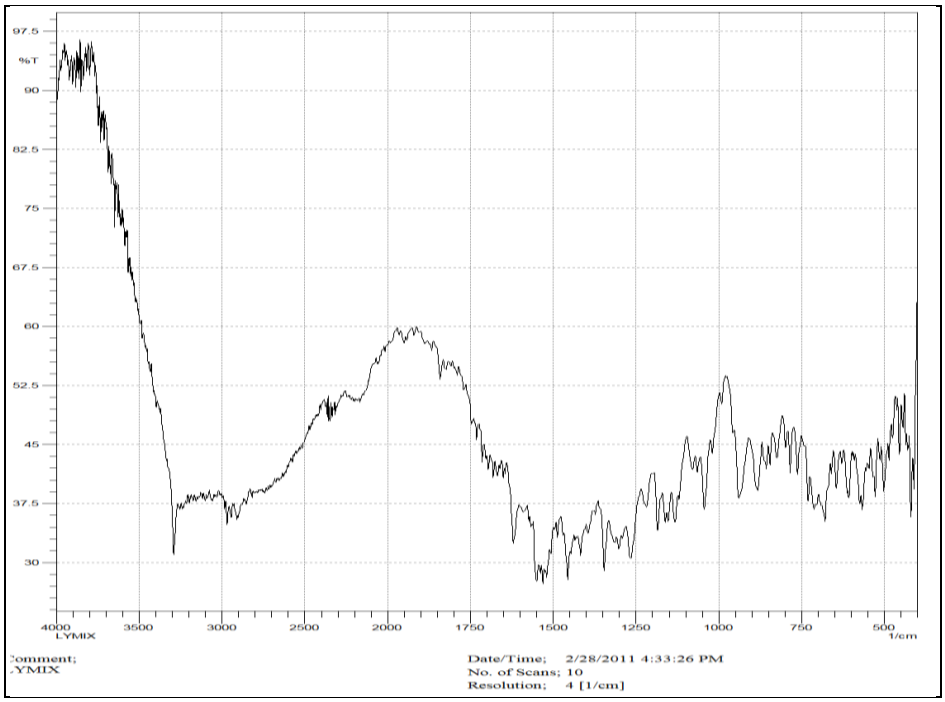

Figure 2: FTIR spectrum for physical mixture for lyophilisation excipients and meloxicam

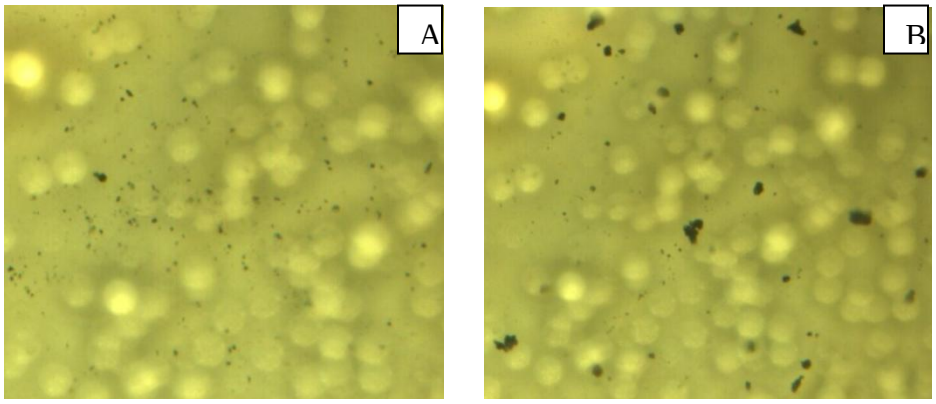

Figure 3: Microscopic images of meloxicam powder in 10x (A) and in 40x (B)

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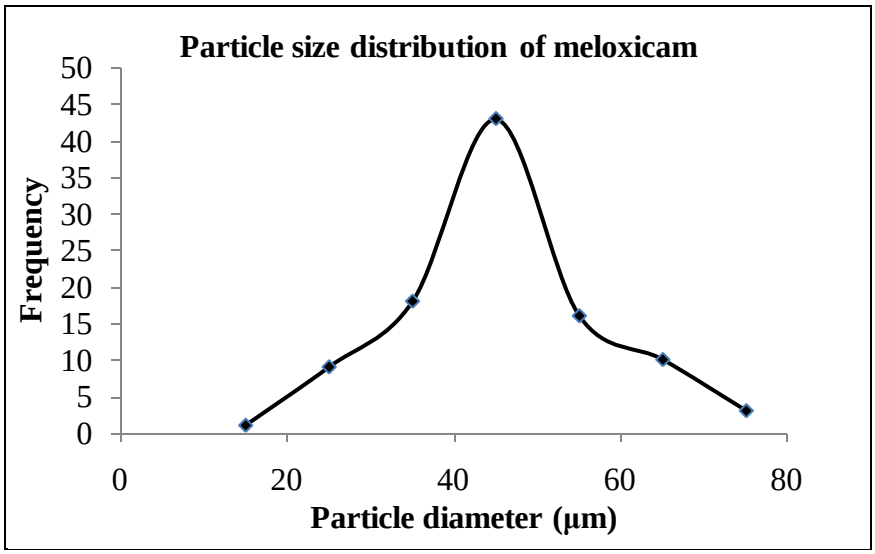

Figure 4: Particle size distribution of meloxicam powder

Selection of gelatine concentration

Increase in disintegration time was observed as the concentration of gelatine increased. It may be because of change in degree of interlinking of molecules of gelatine (Table 6). Hardness of the tablets increased as concentration of gelatine increased. At low concentration of gelatine low degree of interlinking renders the structure fragile as can be seen in G1. Results of moisture analysis showed that moderate increase in the residual moisture content was observed. Reason for that can be given as gelatine being protein in nature contains bound molecules of water in its structure and this binding increases as the concentration of gelatine increase in the solution in water and this increased binding cannot be broken or removed by lyophilization at predetermined process parameters. But in all the batches the moisture content is less than 5% which is desirable and hopefully would not cause any complications during further optimization and formulation. Theoretical weight was calculated based on solid content dissolved in the solution. After drying the weight imparted by the lyophilised tablets (LTs) is because of the total solid contained by unit volume of solution (0.5 ml as for this study). Deviation in the practical wt. of LTs from theoretical wt. might be because of errors in measurement of solution and residual moisture content. The overall physical examination of the LTs showed that in G1 high degree of shrinking and shape deformation is observed. It may be because of less enough solid content in the formulation to support the structure. Moderate shrinking and shape deformation was observed in G2. In G3 shape deformation was negligible and slight shrinking was observed. In G4 very slight shrinking and no shape deformation was observed.

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Table 6: Evaluation of batches for selection of gelatine concentration

Evaluation parameter	Batch			
	G1	G2	G3	G4
DT (sec)	93±2	133±2	161±3	207±3
Hardness (N)	very fragile to handle	4.0±0.5	9.0±0.4	17.0±0.2
Moisture content (%)	0.80±0.02	1.20±0.02	1.60±0.03	1.73±0.02
Theoretical wt (mg)	2.5	5	7.5	10
Practical wt. (mg)	2.6±0.1	5.1±0.1	7.5±0.3	10.0±0.2
Comment	High degree of shrinking and shape deformation	Moderate shrinking and shape deformation	Slight shrinking and no shape deformation	Very low shrinking and no shape deformation

Selection of the LT formulation that is to be taken forward for further study depended on the tablet having sufficient hardness to withstand manual handling, and a disintegration time of less than 3 min: the designated cut off time for this study as per the EU pharmacopoeia.

A measurement called Lyophilized Tablet Index (LTI) is defined that took both the above-mentioned factors into consideration and was used in making a decision as to which batch to take forward.

$$\text{LTI} = \frac{\text{Tablet hardness}}{\text{Disintegration time}}$$

Ideally, the LTI value for a formulation would be as high as possible. However, it is possible for tablets with poor mechanical strength to have high LTI values if their disintegration time is less. Such is the case with the batch G1, which was excluded from the study based on its poor hardness.

The batch G4 was excluded from consideration though it is having highest LTI because it has DT more than 3min. Out of two remaining batches G2 and G3, LTI value of G3 is higher (Table 7). So G3 was selected for further study.

Table 7: LTI values of batches of gelatine

Batch	G2	G3
LTI value	0.030	0.055

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Selection of concentration of glycine and mannitol

The results of disintegration (Figure 5) showed that drastic decrease in the disintegration was observed with incorporation of the saccharides as compared to G3. It might be because of the entrapment of crystals of saccharides in the gelatine strands at molecular level and reduced level of crosslinking of the gelatine molecules. Upon exposure to medium these crystals easily get released in the medium and trigger the disintegration. There is less difference in the hardness of E1 and E2 as compared to G3 (Table 8). It might be because of predominant bonding of gelatine strands then effect of bonding to saccharide crystals. Drastic decrease in the hardness of E5 and E6 was observed. It might be because of higher degree of weaker bonding with saccharide crystals than bonding with gelatine strands. Same reasoning can be presented for higher friability of E5 and E6. Comparing the LTI values the highest value was observed in E4.

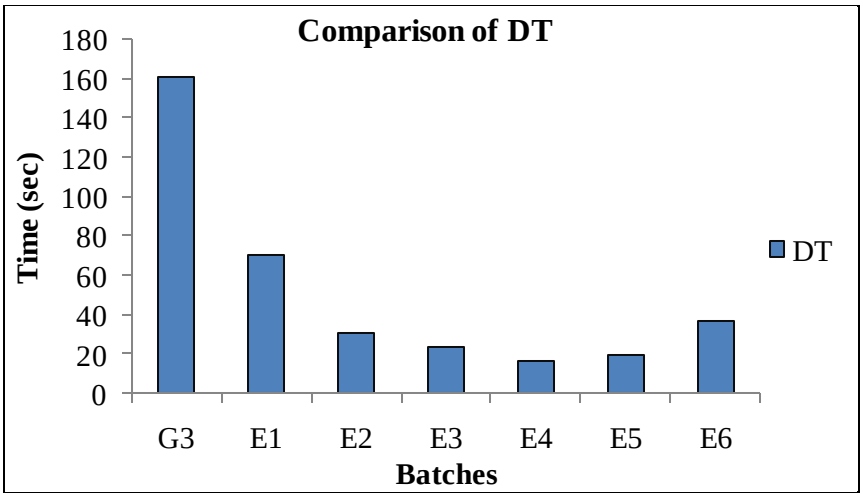

Figure 5: Effect of glycine and mannitol on DT of LTs

Table 8: Evaluation of batches for selection of glycine and mannitol

Evaluation parameter	Batch					
	E1	E2	E3	E4	E5	E6
DT (sec)	70±1	31±2	23±2	16±1	19±2	37±3
Hardness (N)	7.0±0.1	6.0±0.1	6.0±0.1	5.0±0.1	2.0±0.1	2.0±0.2
Moisture content (%)	1.22±0.02	1.31±0.02	2.14±0.03	1.25±0.02	2.31±0.04	2.13±0.03
Theoretical wt (mg)	12.5	17.5	22.5	27.5	32.5	37.5
Practical wt. (mg)	12.9±0.1	17.8±0.1	22.9±0.3	27.7±0.2	32.6±0.1	37.5±0.2
Friability(%)	0.58	0.76	0.97	1.3	2.6	3.2
LTI	0.1	0.19	0.23	0.31	0.105	0.054

Effect of sodium alginate on properties of LTs

Results of disintegration time showed that little increase in disintegration time of N1 was observed as compared to E4 (Table 9). And it showed significant increase in N2 and N3. Viscosity imparted by all the three batches was sufficient enough that no practical problem of settling of meloxicam particles was observed in any of the batch. The increase in the DT can be justified as sodium alginate being polymer in nature produced some degree of matrixing at the end of lyophilization and due to crossinking of the strands it resulted increase in hardness. This crosslinking and matrix forming increased as the concentration of sodium alginate increased which can be seen by increase in hardness and DT in N2 and N3. The wetting time showed very significant increase in N1 through N3 respectively. It can be justified as decrease in porosity of the formulation. The results of assay indicated uniform dispersion of meloxicam particles with insignificant settling during solution preparation and pouring. The LTI values indicated that it is highest in N1. So for further studies N1 will be used as basis for further development of formulation.

Table 9: Properties of LTs with varying content of sodium alginate

Evaluation parameter	Batch		
	N1	N2	N3
DT (sec)	18±3	25±2	41±2
WT (sec)	16±1	34±2	67±3
Hardness (N)	6.0±0.1	8.0±0.3	11.0±0.4
Moisture content (%)	1.45±0.02	2.36±0.50	2.61±0.30
Theoretical wt (mg)	60.0	62.5	65.0
Practical wt. (mg)	61.0±0.7	63.1±0.4	67.2±0.4
Assay (%w/w)	99.2±0.1	99.4±0.4	99.4±0.2
Friability (%)	0.56	0.53	0.54
LTI	0.33	0.32	0.26

Effect of solubiliser on properties of LTs

The results of DT show slight decrease in R1 through R3 (Table 10). It may be because of improved wetting of the amorphous particles developed after lyophilization. Same can be seen in the results of wetting time. Hardness did not show any significant change in the results as compared to N1. Moisture content is also less than 5%. Assay results show the uniformity of dispersion of meloxicam in solution and accuracy in measuring the solution for filling.

The drug release profile (Figure 6) showed that there was vast difference in the release rates of pure drug and release profile of N1. It can be seen that Q15 is 74 in release profile of N1 as compared to the results of direct compression and wet granulation method where the values of Q15 ranged around 40-50%. It proved the effectiveness of the lyophilization method in improving of the dissolution of meloxicam. It might be because of generation of porous structure in LTs and amorphous particles of meloxicam generated by lyophilization process. Significant difference in the release profiles of N1 and R1, R2 and R3 can be seen. The increase in dissolution is rendered by the solubilising effect of SLS. Though release profiles of R1, R2 and R3 goes similar, Q5 value is highest in R3.

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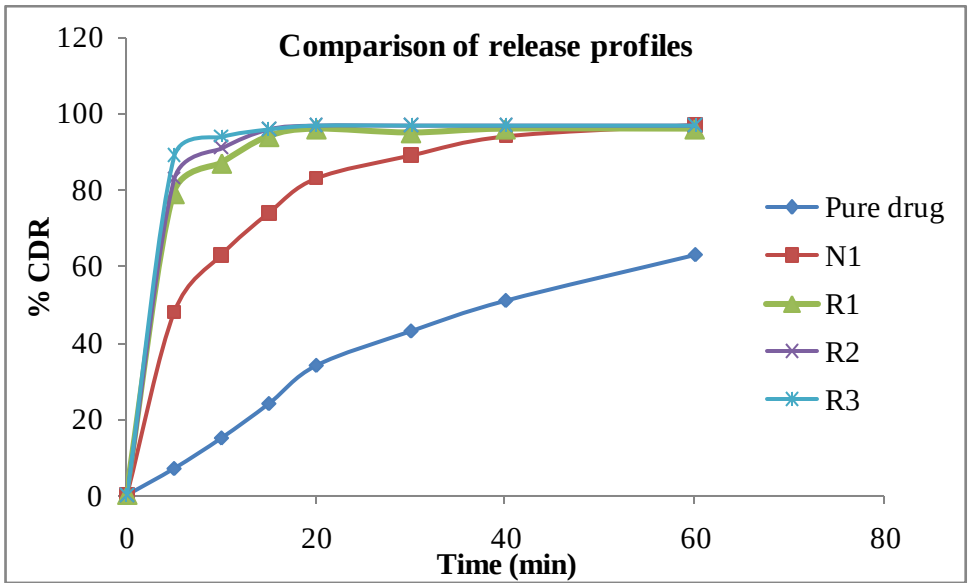

Figure 6: Effect of SLS on dissolution properties of LTs

Table 10: Properties of LTs with varying content of SLS

Evaluation parameter	Batch		
	R1	R2	R3
DT (sec)	16±1	16±2	14±1
WT (sec)	14±1	11±1	10±1
Hardness (N)	6.0±0.1	6.0±0.3	6.0±0.2
Moisture content (%)	1.42±0.02	1.26±0.50	1.44±0.30
Theoretical wt (mg)	60.5	61.0	61.5
Practical wt. (mg)	61.0±0.2	62.3±0.4	63.1±0.4
Assay (%w/w)	99.4±0.2	99.2±0.3	99.1±0.1
Friability (%)	0.46	0.49	0.45
Q5	79±1	83±2	89±2

Effect of tweens on properties of LTs

Results of DT showed that incorporation of tweens had significantly decreased the disintegration time of R3 (Table 11). But the change in concentration did not have majorly changed the results of DT. The wetting times of the all batches had significantly decreased in all the batches. This confirmed the effectiveness of the tweens in wetting the porous structure of the LTs. It might be because of instant penetration of the medium in the porous structure of the LTs which immediately disintegrates the tablets within few seconds. Results of moisture content showed that there is significant increase in the residual moisture content in T2, T3 and T4. It can be justified as at higher concentration tweens might have hindered the sublimation of water at latter stage of lyophilization mainly because of their very low vapour pressure. It can be seen in T2. In T3 and T4 moisture content was even higher which might be the result of higher viscosity of tween 80 then tween 20. The friability results show increase in T2, T3 and T4. It may be because of hindrance of molecules of tweens in bonding with polymer strands and

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crystals subsequently developed during lyophilization. Drug release profiles didn't show any significant change.

Table 11: Properties of LTs with disintegration enhancer

Evaluation parameter	Batch			
	T1	T2	T3	T4
DT (sec)	8±1	10±2	9±1	10±1
WT (sec)	5±1	5±1	4±1	4±1
Hardness (N)	6.0±0.1	5.5±0.2	5.2±0.1	5.3±0.1
Moisture content (%)	1.42±0.02	4.21±0.50	3.63±0.30	4.15±0.20
Theoretical wt (mg)	62.0	62.5	62.0	62.5
Practical wt. (mg)	63.7±0.2	64.3±0.4	64.3±0.3	64.7±0.5
Assay (%w/w)	99.3±0.3	99.5±0.2	99.4±0.4	99.2±0.3
Friability (%)	0.51	0.67	0.54	0.71
Q5	88±3	89±1	89±2	91±1

By reviewing above results the batch T1 was selected to be the optimized batch developed by whole of the lyophilization process. Figure 7 shows the morphology of the prepared tablets of the optimized batch and Figure 8 shows the SEM image of the optimized batch. The porous structure can be seen in the image.

Figure 7: Shapes of lyophilized tablets from different angles

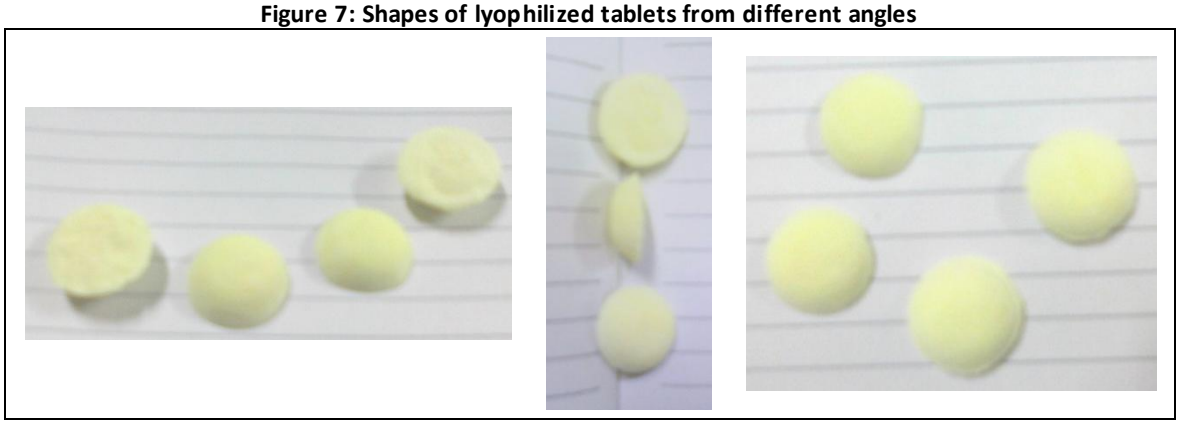
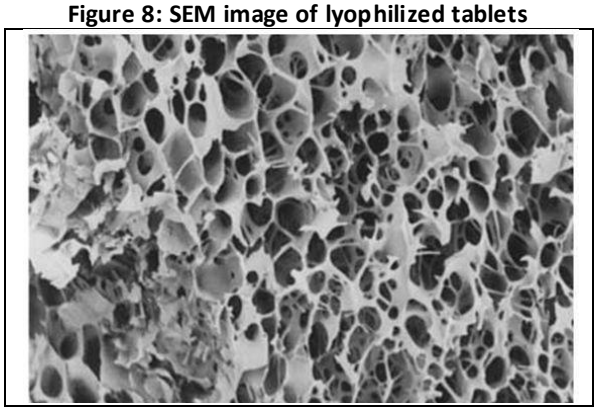


Figure 8: SEM image of lyophilized tablets



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CONCLUSION

Lyophilisation method was successfully used to prepare the fast dissolving tablet of meloxicam. Significant increase in dissolution of meloxicam was observed using SLS at 0.3 %W/V. Disintegration time of batch T1 as low as 8 sec showed effectiveness of tween20 in decreasing disintegration time of tablets with sufficient strength. the developed formulation of fast dissolving tablet of meloxicam can be further developed for improved patient compliance and efficacy.

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