Research Article

A Novel Practical Approach for Enhancement of Bioavailability of A Poorly Water Soluble Drug By Hot Melt Coating Technique

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ABSTRACT

Bioavailability of drugs with low solubility and high permeability can be increased remarkably by improving solubility. One of the most widely used technique for this is formulation of solid dispersions. Solid dispersions suffer from the practicability of large scale processing into suitable formulations. Solid dispersion of anti-inflammatory drug, Meloxicam (ME) with different ratios of Stearoyl macrogolglyceride (Gelucire 50/13), PEG 4000, PEG 6000, PEG 20000, PVP K-30 and Polaxomer (Lutrol F 68) were prepared by melting method. Hot melt coating of this solid dispersion on inert pellets was explored in this study as a mean to improve the dissolution and subsequent bioavailability. IR spectroscopy, X-ray diffractometry and in vitro dissolution were used to evaluate the characteristics of coated melts. The physical mixture and melts show similar IR and XRD spectra in all cases. The in vitro dissolution in pH 1.2 HCl and pH 7.4 phosphate buffer media showed remarkable improvement in drug dissolution especially with Gelucire 50/13. Solid dispersions, hot melt coated on inert substrate can be a novel and practical approach for enhancement of bioavailability of drugs with low water solubility.

Keywords: Gelucire 50/13, Hot melt coating, Meloxicam, PEG, Solid dispersion, Solubility enhancement.

INTRODUCTION

Solubility enhancement and subsequent improvement in bioavailability of drugs remains one of the most demanding aspects in formulation development.[1] The methods other than chemical modification for dissolution improvement was first used by Sekiguchi and Obi in which eutectic mixtures were utilized for dissolution improvement which was then termed as solid dispersion (SD).[2-5] Later, preparation of SD was investigated for many drugs.[6-9] Though formulation of SD appear to be very promising at laboratory scale, the scale up and commercial application of SD in dosage form design has been very limited and few products have been successfully marketed.[10] The method of preparations, the formulation into dosage forms, and the scaling-up processing of SD system all involve limitations.

Hot melt coating (HMC) involves application of molten coating materials on the substrate surface.[11-12] HMC has many advantages like use of solvents, shortened processing time. HMC has found many applications in pharmacy from simple protective coating to release controlling coating.[13-15] The study was undertaken with the aim of evaluating the hot melt coating method for the preparation of one step formulations of SD applied directly on non peril seeds (NPS). This will not only increase the dissolution of poorly water-soluble drugs but also simplify the formulation process, which further would help in overcoming the difficulties generally faced during scaling-up of the SDs.

Meloxicam (ME), a BCS class II drug, is a potent non-steroidal anti-inflammatory drug (NSAID), has been extensively investigated for developing SDs using various Solubilizing materials and with different methods and was selected as a model drug for this study.[8,16-20] Though Gelucires are widely used as solubility enhancers its physicochemical properties make it a first choice for preparing SDs and subsequent hot melt coating.[21-24]

MATERIALS AND METHODS

Materials

Meloxicam was received as research sample from Lupin Ltd., Pune, India. Particle size of Meloxicam provided was specified as not less than 90% of particles below 15 micron. Stearoyl macrogolglyceride (Gelucire 50/13) was gifted by Gattefosse (Cedex), France. Lutrol F 68 and PVP K-30 was generously gifted by Signet, India. PEG 4000, PEG 6000 and PEG 20000 were purchased from S.D. Fine chemicals, Mumbai, India. All other chemicals were of analytical grade and were used as received.

Methods

Hot melt coating of non peril seeds (NPS)

As shown in Table 1, the drug (ME) and wax were mixed in predefined proportions in a clean 100 mL beaker. The mixture was melted by heating at 5°C/min increment using hot plate and was maintained in molten state with continuous stirring using magnetic stirrer. For hot melt coating, modified coating spray gun was used. (Figure 1)

NPS were feed to the coating pan rotating at a speed of 35 rpm and the molten mixture was spread over cascading NPS bed with coating gun from a distance of

about 5 inches from bed. The air pressure was 60 lb/m^2 and the temperature was maintained about 3°C above melting point of wax. The process was carried out to coat about 2 % w/w drug on the NPS.
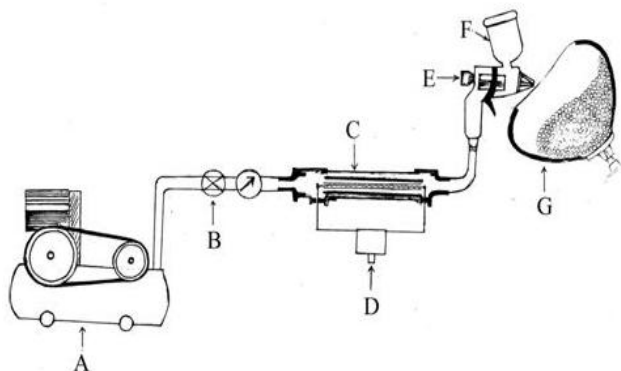

Figure 1: Modified spray gun for hot melt coating A- Air compressor, B- Pressure regulator, C- Heating unit, D- Thermostat, E- Spray gun, F- Feed reservoir, G- Coating pan.

Preparation of physical mixture (PM)

For the preparation of a ME–wax physical mixture (PM), ME and wax were weighed and mixed for 5 min using a pestle and mortar and sieved through a 400 μm mesh. About 60 mg of ME–wax powder mixture (containing 15 mg of ME and 45 mg of wax) was filled into a hard gelatin capsule (size 2) for further investigations.

Scanning electron microscopy

The pellets coated with SD were sputtered with gold for 5 min using a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan). The surface was examined by scanning electron microscopy (SEM, Jeol JSM 5600 LV, Jeol, Tokyo, Japan) at 10 kV.

X-ray diffraction

X-ray powder diffractometry (XRD) was performed with a Philips X-ray diffractometer (PW 1050/70 PW 1710). The measurement conditions were radiation source, CuKα; scan speed (2θ/s), 0.035; step size (2θ/s), 0.035; and time per step, 1.0 s.

IR spectroscopy

Drug, physical mixture and Melts were analyzed by infra red spectrophotometry using shimadzu IR spectrophotometer (FTIR-8001, Shimadzu, Japan) for evaluating interaction. Only ME:PEG 6000 and ME: Gelucire 5013 in the ratio 1:3 were evaluated for XRD and IR studies based on the results of dissolution study.

Evaluation of pellets

Drug content

100 mg pellets were accurately weighed and transferred to 100 mL volumetric flask containing 60 mL acetone and sonicated for 15 minutes, volume was made up to 100 mL with distilled water and filtered. 5 mL of this solution was diluted with 5 mL 0.1 N sodium hydroxide solution and analyzed by UV spectrophotometer at 362 nm (Shimadzu, Japan, Model No.1601).

Dissolution study

Pure ME, PM and hot melt coated NPS were evaluated for dissolution studies. The PM, coated NPS and pure ME as reference sample were filled into hard gelatin capsules (size 2). Dissolution tests were performed using USP type I dissolution test apparatus at 100 rpm using 0.1N HCl. Samples were withdrawn at 5, 10, 20, 30, 60 and 90 min interval and were assayed spectrophotometrically at 362 nm.

RESULTS AND DISCUSSION

Photograph shows that coated NPS retained a spherical shape and a smooth surface was observed in SEM. Further magnification of the surface of pellet did not show presence of drug crystal indicating completely embedded drug in the vehicle (Figure 2). The coating was uniform and the drug content in all the batches was found to be within the range of ±5% of the theoretical claim. Estimated lower standard deviation in the data indicates that the drug was distributed uniformly in the batch and the scheme used was steadfast and imitable.
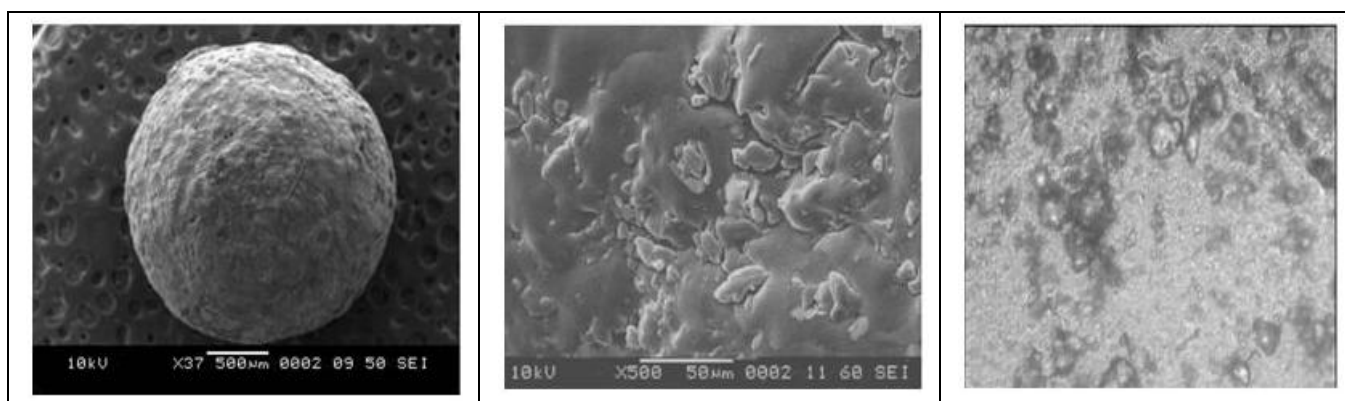

Figure 2: Scanning electron microphotographs of ME:Gelucire 50/13 coated pellets at different magnification (37 X, 500 X and 1500 X).

Table 1: Composition of solid dispersion for hot melt coating

Batch	Meloxicam	Dispersion Ratio	PEG4000	PEG6000	PEG20000	Gelucire 50/13	Polaxomer (Lutrol F68)	PVP K30
1	1	1:3	3	-	-	-	-	-
2	1	1:5	5	-	-	-	-	-
3	1	1:10	10	-	-	-	-	-
4	1	1:3	-	3	-	-	-	-
5	1	1:5	-	5	-	-	-	-
6	1	1:10	-	10	-	-	-	-
7	1	1:3	-	-	3	-	-	-
8	1	1:5	-	-	5	-	-	-
9	1	1:10	-	-	10	-	-	-
10	1	1:1	-	-	-	1	-	-
11`	-		-	-	-	2	-	-
12	-		-	-	-	3	-	-
13	1	1:5	-	-	-	5	-	-
14	1	1:10	-	-	-	10	-	-
15	1	1:3	-	-	-	-	3	-
16	1	1:5	-	-	-	-	5	-
17	1	1:2.8:0.2	-	-	-	2.8	-	0.2
18	1	1:3	-	-	-	3	-	-

The dissolution profile of pure drug was first studied and equated with ME:Gelucire 50/13 SD in various ratios. Fig. 3 presents the dissolution profiles of the pellets coated with molten ME-Gelucire 50/13 mixture in 1:1, 1:2, 1:3, 1:5 and 1:10 ratio in 0.1 N HCl.
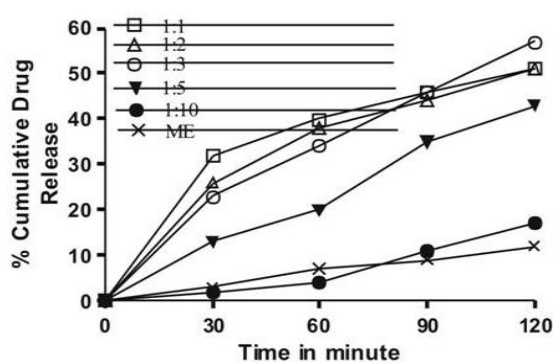

Figure 3: Dissolution profile of ME:Gelucire 50/133 complex with different ratio. (☐), 1:1; (△), 1:2; (⊖), 1:3; (▼), 1:5; (●), 1:10; (✕), ME.

For pure ME the wettability of the particles was very low since ME is a poorly water soluble drug. The amount of drug released in 1 hr and 2 hr respectively was found to be 7% and 12% for pure drug, 40 and 48%, 38 and 48% for 1:1 and 1:2 ratio of ME:Gelucire 50/13. Surprisingly there was no significant effect of increasing ME:Gelucire ratio from 1:1 to 1:2. The drug:Gelucire 50/13 ratio of 1:3 was found to be most efficient in increasing dissolution of ME showing 57% dissolution in 2 hours. It was also observed

that the dissolution rate decreases if the concentration of incorporated Gelucire 50/13 was increased above 3 times of drug content. The drug dissolution was merely 43% in two hours at 1:5 ratio which further reduced to 17% at 1:10 ratio. Increased Gelucire 50/13 content beyond 1:5 ratios instead of aiding solubility might have resulted in formation of matrix like structure, resulting in decreased dissolution. Although the drug dissolved from ME-Gelucire 50/13 SD at 1:10 ratio was lower than all other combinations, till it was comparatively higher than pure drug revealing that the surface drug was till dissolved faster due to Gelucire 50/13 than pure drug.

For evaluating comparative efficiencies of drug:Gelucire 50/13 in 1:3 ratio with other solubility enhancing materials pellets were coated with 1:3 ratio of PEG 4000, PEG 6000 and PEG 20000. Dissolution of the aforementioned batches was carried out in pH 7.4 Phosphate buffer as this buffer media was extensively used in previous studies. All the pellets batches showed remarkable improvement in dissolution in this pH and Gelucire 50/13 being most efficient with 94% dissolution of ME in two hours. The dissolution profile in pH 7.4 is shown in Figure 4.

PEG 6000 released 88% drug in 2 hours and no significant difference was observed between Gelucire 50/13 and PEG 6000 dissolution profiles. PEG 20000 showed 74% dissolution and followed by PEG 4000 with 70 % dissolution. Pure ME showed a mere 22% dissolution in 2 hours at this pH.

To get a precise idea about efficacy of SD, differentiating media dissolution was carried out at 1.2 pH. The dissolution profile in pH 1.2 is shown in Fig. 5.
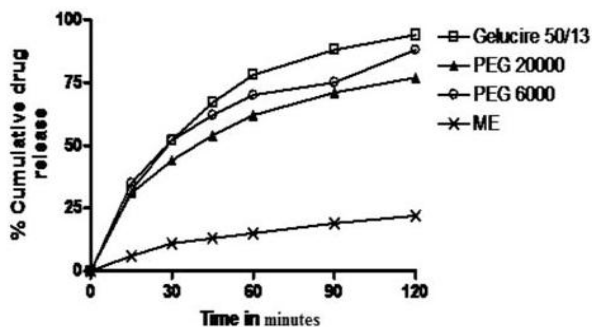

Figure 4: Dissolution profile of ME complex with different waxes in pH 7.4 phosphate buffer in 1:3 ratio. (—□—), Gelucire 50/13; (—▲—), PEG 20000; (—○—), PEG 6000; (—✕—), ME.
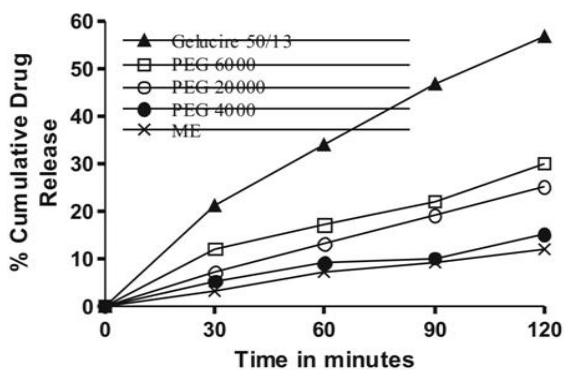

Figure 5: Dissolution profile of ME complex with different waxes in 1.2 pH in 1:3 ratio. (—▲—), Gelucire 50/13; (—□—), PEG 6000; (—○—), PEG 20000; (—●—), PEG 4000; (—✕—), ME.
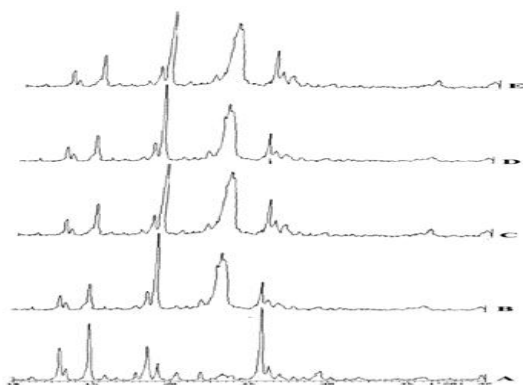

Figure 6: X-ray diffractogram A- ME, B- ME-Gelucire 50/13 PM, C- ME-Gelucire 50/13 SD, D- ME-PEG PM, E- ME-PEG SD.

The pellets coated with PEG 4000:ME mixture showed only 15% dissolution in two hours and PEG 20000 showed only 25 % dissolution. Amongst the PEGs evaluated PEG 6000 showed most efficient improvement in dissolution

of ME giving 30 % dissolution in two hours. Thus none of the evaluated PEG was able to improve dissolution as Gelucire 50/13 which showed 57% dissolution in two hours i.e. nearly 4.5 times higher than plain ME. SD of ME with PVP K 30 and Lutrol F 68 does not shown significant improvement in the dissolution compared with PEGs even above 1:5 ratio of ME:PVP K 30 and ME:Lutrol F 68. The x ray diffraction data (Figure 6)

reveals that there seems to be no apparent change in diffraction pattern of physical mixture and SD and the observations are similar to those interpretations reported recently by Bashiri-Shahroodi et al 2008 (Nassab, 2006; Bashiri-Shahroodi, 2008).[2] Relative crystallinity can be determined by comparing some representative peak heights in the diffraction patterns of the binary systems with a reference as per the formula;

Relative degree of crystallinity (RDC) = I_{sam} / I_{ref} ,

Where, I_{sam} is the peak height of the sample under investigation and Iref is the peak height at the same angle for the reference with the highest intensity.

Pure drug peak at 25.7∘ (2θ) was used as I_{ref} for calculating RDC of physical mixture and SD.

Sample	Peak intensity at 25.7° (2θ)	RDC
ME plain	441	---
ME-PEG 6000 PM	216	0.489
ME-PEG 6000 SD	216	0.489
ME-Gelucire 50/13 PM	339	0.768
ME-Gelucire 50/13 SD	286	0.648

* PM- physical mixture, SD- Solid dispersion

The RDC values of corresponding pattern are similar to that of pure ME but with relatively less intense peaks. In the case of ME-PEG 6000 PM and ME-PEG 6000 SD samples a similar diffraction pattern was observed irrespective of method of treatment indicating no change in crystallinity. In the case of the ME-Gelucire 50/13 PM and ME-Gelucire 50/13 SD showed a diffraction pattern similar to that of pure ME, but with a reduction in peak intensities was more in case of SD than PM this reduction might be due to change in crystallinity. The SD formulations were substantially identical to that of PM, and only little variations in the intensity of the signals were noticed, indicating a lack of a well defined interaction between the drug and the carrier in their solid state. Previous studies also reported that though x ray diffraction studies show that melt dispersion and physical mixture of ME:PEG 4000 shows similar XRD pattern and further treatment of XRD data by chemometric analysis-self modeling curve resolution and Borgon plot reveals presence of the new crystalline phase, due to molecule-molecule cluster overlapping no disparity was observed in the diffraction pattern. This might be true also for Gelucire SD.[2]
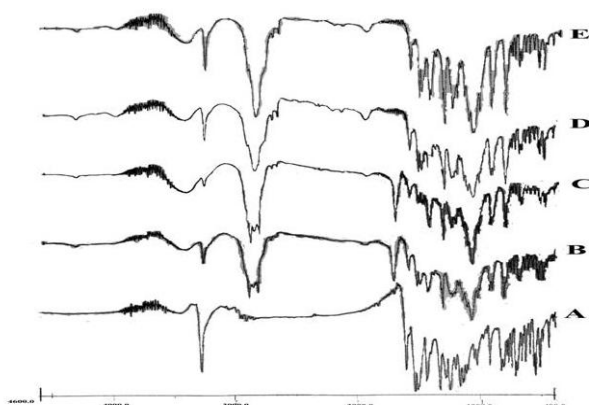
Figure 7: IR-spectra A- ME, B- ME-Gelucire 50/13 PM, C- ME-Gelucire 50/13 SD, D- ME-PEG PM, E- ME-PEG SD.

In IR spectroscopy (Fig. 7), the drug showed peaks at 3291.0 cm−1 for NH asymmetric and symmetric stretching vibrations , 2918.7 cm^{-1} for CONH, 1620.4 cm^{-1} for SO_2, 1551 cm^{-1} for coupling N-H bending and C-N stretching vibration, peaks between 527.2 and 1452.9 cm^{-1} characteristic aromatic ring. Physical mixtures exhibited peaks of the drug and the carriers. The chemical structure of Gelucire 50/13 suggests that possible interaction would be hydrogen bonding between the hydroxyl group of the polymer and the carbonyl functions of ME. The FTIR spectrum of Gelucire 50/13 presents a large band in the region 3650–3100 cm−1, due to the free O–H stretching vibration of the COOH groups, and a peak at 1737 cm−1 for the C=O vibration. The FTIR spectra of ME-Gelucire 50/13 physical mixtures and of the corresponding SD are almost superimposable; no shifts of all the characteristic peaks of the drug and of the carrier are evident, suggesting the lack of significant interactions. Moreover, the permanence of the drug in its original form was confirmed by this analysis.

CONCLUSION

Hot melt coating of ME using different ratio with Gelucire 50/13 and various grades of PEGs was carried out. Gelucire 50/13 in the ratio of 1:3 with ME showed remarkably enhanced solubility as compared to other solubility enhancers evaluated. Increase in quantity of Gelucire 50/13 above three times of that ME had shown decrease in dissolution due to formation of matrix like structure. FTIR studies confirmed that no significant interaction exists between ME and Gelucire 50/13. Among various grades of PEGs evaluated as solubility enhancer, PEG 6000 had given satisfactory results for the solubility enhancement of ME. The study indicates that hot melt coating can be a viable option for the preparation of formulations with SD.

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