Application of Polyglycolized Glycerides in Protection of Amorphous Form of Etoricoxib during Compression

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Polymorphic transition and stability problems during amorphous drug formulation are the major limiting factors in pharmaceutical technology. The purpose of the study was to evaluate the ability of polyglycolized glycerides (Gelucire) in protection of amorphous form of drug during compression and shelf life with lower proportion. Amorphous etoricoxib (AET) was prepared by spray drying technique. Tablets of AET and melt granules of AET (MG-AET) with Gelucire 50/13 were prepared. Tablets parameters like hardness, disintegration and content uniformity were evaluated. Tablets were evaluated immediately after compression and on storage for 3 months at ambient conditions to determine degree of transformation using X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and dissolution profiles. Spray drying yielded the amorphous etoricoxib. Content uniformity in the tablet was in between 95 to 105%. Other parameters like disintegration and hardness were well within the limits. The results showed significant difference in the degree of crystallinity between AET tablet and MG-AET tablet. MG-AET tablet showed absence of crystallinity after 3 months storage. The reason could be formation of hydrogen bonding between the Gelucire and AET. Also Gelucire can be tableted very easily under low pressure and showed elastic recovery. Gelucire yielded a soft embedding during tableting, which prevented the polymorphic transformation. Polyglycolized glycerides (Gelucire 50/13) are able to protect amorphous etoricoxib during compression. As excipient required is low, it became possible to prepare tablet formulation as compared to other excipient like polyvinylpyrrolidon (PVP).

Key words polyglycolized glyceride; amorphous; stabilization; compression

Amorphous form of poorly water-soluble drugs lead to marked improvement in their dissolution and thus their relative bioavailability. Many reports on preparation and stabilization of amorphous form have been documented in the literature. Solid dispersion of itraconazole, prepared by spraying the drug and hydroxypropyl methyl cellulose (HPMC) on neutral pellets using organic solvent, is marketed in the trade name of Sporanox®. Similarly solid dispersion of griseofulvin in PEG (Gris-PEG, Novartis) and Nobilon in povidone (Cesamet, Lilly) was marketed.

Despite of this its commercial potential has been limited because of problem in processing of solid dispersions in the suitable dosage form like tablet. Development of solid dispersion into convenient dosage form for their clinical use and successful commercialization is a major challenge for pharmaceutical scientists. Amorphous drug prepared by super critical fluid precipitation has been formulated in the inhalers/spray. Akbuga *et al.* reported tablets of furosemide-PVP solid dispersion but it has limitations like large amount of disintegrants were required for disintegration of tablet[2)] compression difficulties were encountered due to sticking to punches and dies.[3)] Pirttimaki *et al.* reported the polymorphic transformation of caffeine in the tableting,[4)] because during tableting material obtains energy from mechanical pharmaceutical operations like mixing, grinding, granulation, drying and tableting necessary for transformation.

In an effort to prevent polymorphic transformation of amorphous indomethacin and stabilization of enzymes, Picker *et al.* has evaluated carrageenan, a polymer with high viscoelastic property. It was found to be superior to microcrystalline cellulose, the effect was attributed to the high elasticity of carrageenan during tableting.[5—7)] Schmidt *et al.*[8)] have reported the potential of polyethylene oxides for protection of amorphous indomethacin due to tableting. Similarly, heterogeneous system containing lipids has been reported for enzyme stabilization in the tablet form.[9)] Recently, Shimpi *et al.*[10)] have reported stabilization of amorphous form of etoricoxib in the melt granules with low amount of polyglycolized glycerides (Gelucire) 50/13. The stabilization has been attributed to H-bonding between Gelucire and drug and immobilization of the molecule in the matrix.

In the present study it is hypothesized that Gelucires can offer elasticity and protects amorphous form during compression and shelf life. Aim of the present study was to evaluate the effect of compression on the stability of amorphous etoricoxib. Our earlier study on the melt granules revealed that Gelucire 50/13 has the stabilizing ability for amorphous etoricoxib in the ratio of 1 : 0.5 w/w.

Experimental

Materials Etoricoxib (ET) was obtained as a gift sample from Unichem Laboratories Ltd. (Mumbai, India). Gelucire® 50/13 (Stearoyl Macrogoglycerides EP, Gattefosse, France) and Avicel PH 102 (microcrystalline cellulose) were supplied by Colorcon India (Mumbai, India) and Get Rid Pharmaceutical (Pune, India) respectively. All other chemicals were of analytical grade.

Methods. Preparation of Amorphous ET (AET) ET was dissolved in methylene chloride (10% w/v). The clear solution was spray dried on a spray drier (Jay Instruments & Systems Pvt. Ltd., Mumbai, India) under following set of conditions: flow rate, 10 ml/min; inlet temperature, 90 °C; outlet temperature, 70—75 °C; aspiration −300 mm WC and atomization air pressure, 2 kg/cm^2. The resulting solid was placed in a vacuum dryer for 24 h to remove residual solvent.

Preparation of Granules Granules of AET (MG-AET) were prepared using the melt granulation technique. The drug : lipid ratios used to prepare the granules were 1 : 0.5 parts by weight. Lipid was melted at 60 °C. To the molten lipid AET was added, mixed well then cooled to room temperature to obtain the solid mass. The mass was passed through 510 μm sieve to obtain uniform sized granules.

Preparation of Tablet AET and MG-AET were further compressed

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Table 1. Tablet Parameters

Parameters	AET Tablets		MG-AET Tablets	
	Initial	3 month, 30 °C/65%RH	Initial	3 month, 30 °C/65%RH
Hardness	5±1 KP	5±1 KP	5±1 KP	5±1 KP
Thickness	2.3±0.2 mm	2.3±0.2 mm	2.4±0.2 mm	2.4±0.2 mm
Friability	<0.2%	<0.2%	<0.2%	<0.2%
Disintegration time	<6 min	<6 min	<4 min	<4 min
Dissolution at 30 min	42.7%	24.9%	81.4%	81.2%
Dissolution at 60 min	55.4%	35.8%	94.5%	92.8%

using Avicel PH 102 as diluent at a constant weight (240 mg) and pressure using single rotary multi-station compression machine (Rimek, Karnawati Engineering Pvt. Ltd., Ahamedabad, India) using 8 mm punch set.

Tablet Parameters Tablets were evaluated for hardness (Incorp Ltd., Hyderabad, India), friability (Electrolab, Mumbai, India) and disintegration (Electrolab, Mumbai, India). To study the segregation behavior of MG-AET during tableting, content uniformity was analysed.

Thermogravimetric Analysis (TGA) In order to calculate the amount of residual methylene chloride in the spray dried drug and solid dispersions, thermogravimetric analyses were performed using TA-60WS Thermal gravimetric analyzer (Shimadzu Corporation, Japan). Samples of approximately 30—40 mg were heated in platinum crucible in nitrogen atmosphere and the loss of weight was recorded.

Differential Scanning Calorimetry (DSC) DSC studies were performed using Mettler-Toledo DSC 821^{c} (Mettler Toledo, Switzerland) instrument equipped with an intracooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in an aluminum pan and heated at a constant rate of 10 °C/min, over a temperature range of 25—170 °C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 ml/min. Sample weights were in the range of 5 to 10 mg.

X-Ray Powder Diffraction (XRPD) X-Ray powder diffraction patterns were recorded on X-ray diffractometer (PW 1729, Philips, The Netherlands). The samples were irradiated with monochromatized Cu$K\alpha$ radiation (1.542 Å) and analyzed between 2 and 50° 2θ at ambient temperature. The voltage and current used were 30 kV and 30 mA respectively. The range and the chart speed were 5×10^{-3} CPS and 10 mm/° 2θ respectively.

Dissolution Studies The dissolutions were investigated in triplicate. Studies were carried out in USP 24 type II dissolution test apparatus (TDP-06P, Electrolab, Mumbai, India) with the agitation speed of 100 rpm in phosphate buffer (pH 6.8) maintained at 37±0.2 °C. At appropriate time intervals, samples were withdrawn and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no. 41, concentration of ET was determined spectrophotometrically at 232.2 nm with suitable dilutions. Analysis of data was done using PCP-Disso software (V3, Poona College of Pharmacy, Pune, India).

Stability Study The stability of samples was monitored up to 3-month at ambient temperature and relative humidity (30 °C/65% RH). Periodically samples were removed and characterized by dissolution along with presence of crystallinity by XRPD studies. Dissolution studies of stability was carried out to study the changes occurred during stability. Physical parameters like hardness, friability and disintegration time were also evaluated.

Result and Discussion

Optimization of parameters for spray drying was carried out on the basis of % yield. The yield of spray drying was 80—85% AET. The amount of organic solvent in the dried particles was below the detection limit of TGA (<0.05% w/w). The initial characterization of the AET showed a hump in the XRPD pattern and characteristic DSC thermograms with change in heat capacity at 42 °C indicating glass transition temperature (T_g). Glass transition temperature refers to the point at which the super cooled melt, freezes into a solid state known as a glass with increased viscosity compared to the 'rubbery' state at temperatures above the T_g. T_g was followed by recrystallization exotherm at 108 °C and melting

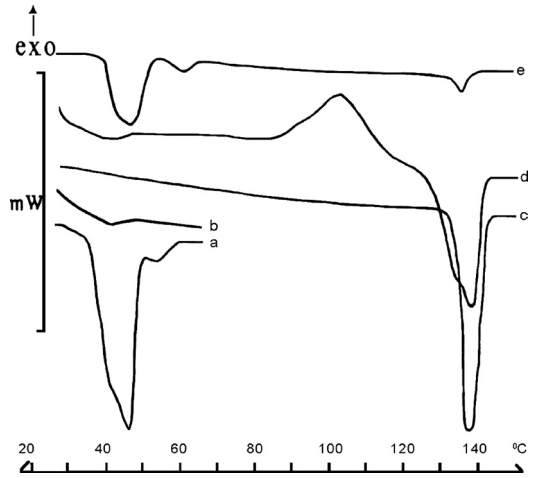

Fig. 1. DSC Thermograms of Initial Samples

Key: Gelucire 50/13 (a); AET showing T_g (b); ET (c); AET (d); MG-AET, 1 : 0.5 (e).

endotherm at 138 °C. DSC pattern of MG-AET showed broad melting peak of the Gelucire 50/13 at 51 °C followed by the small melting peak at 138 °C (ΔH=7.8 J/g) as compared to ET alone (139 °C; ΔH=82.68 J/g), which indicated presence of amorphous form (Fig. 1). The T_g might have overlapped with the melting peak of the lipid.[11)]

Tableting process was well defined and reproducible. Tablet hardness and friability was well within the limit. Tablet was disintegrated within the limit, specified for uncoated tablet in the pharmacopoeia. Content uniformity of the MG-AET granules was analyzed. The ET content in each tablet was 95 to 105%, which is well within the acceptable limit.

Dissolution profiles of ET, AET, MG-AET, AET tablet, and MG-AET tablet in phosphate buffer (pH 6.8) are shown in Fig. 2. It shows that 51% AET was dissolved in 60 min as compared to 35% for ET. Dissolution profiles of MG-AET showed that 93% as compared to melt granules of crystalline ET (77%, data not shown) in 60 min. This clearly indicated that Gelucire played an important role in improvement of dissolution rate of drug. Here the improvement in dissolution was attributed to two factors *viz.* the presence of amorphous form in the granules and hydrophilicity of lipid. Though Gelucire increased dissolution of drug, increase in Gelucire proportion from 0.5 to 1 did not have any significant effect (data not shown). Both amorphization and melt granulation with Gelucire are important factors for improving the dissolution rate. This technique assures presence of amorphous form, whereas spray drying of drug with low melting excipient like lipids and polyethylene glycols showed presence of

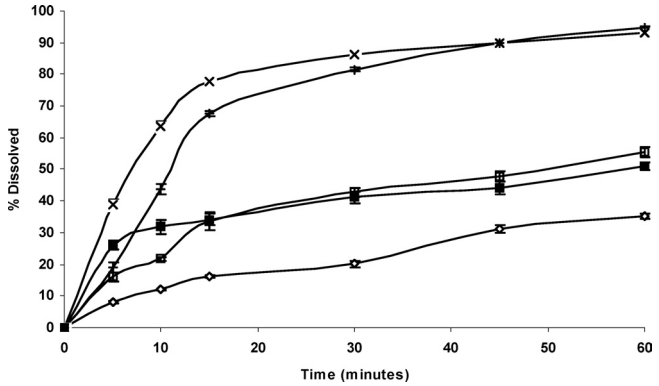

Fig. 2. *In Vitro* Dissolution Profile of Initial Samples

Key: ET (◇); AET (□); AET tablet (■); MG-AET, 1 : 0.5 (×); MG-AET, 1 : 0.5 tablet (+).

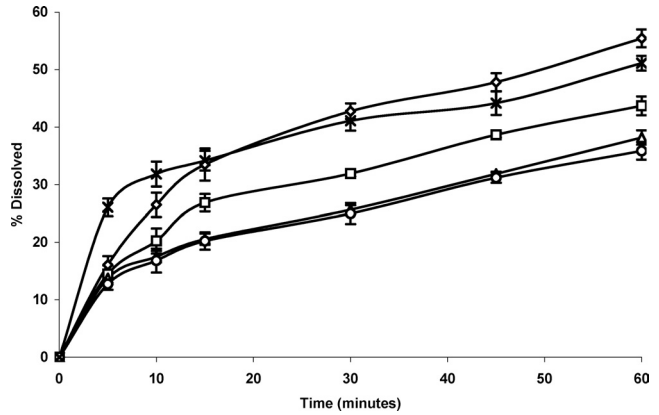

Fig. 3. *In Vitro* Dissolution Profile of AET Tablet Stability Samples

Key: AET (◇); AET tablet, initial (×); AET tablet, 10 d (□); AET tablet 30 d (△); AET tablet, 90 d (○).

partial crystalline form that increases on storage.[12)]

The dissolution of AET and MG-AET tablets showed initial decreased dissolution rate due to time required for tablet disintegration but the overall dissolution has improved slightly as compared to AET and MG-AET. This might be attributed to the presence of excipient, which aided the dispersibility of the AET and MG-AET. Thus immediate effect of compression on crystallinity could not be evaluated by dissolution rate; it was studied using the XRPD patterns, which is discussed later.

The dissolution profile for the stability sample revealed that there was significant decrease in dissolution from AET tablet (Fig. 3). Dissolution profile of 3-month stability sample of AET was matching with the dissolution profile of crystalline drug. Figure 4 shows the dissolution profile of the stability sample of MG-AET tablet. No significant decrease in the dissolution profile was observed. This clearly indicated that amorphous form of ET is stable in the MG-AET tablet.

XRPD patterns of AET and MG-AET at different time period are shown in Figs. 5 and 6 respectively. The diffraction peaks at 16.4, 18.2, 22.6, 24.1 28.8° 2θ were the characteristic peaks of crystalline ET. Among these peaks, 16.4, 18.2, 28.8° 2θ were considered to be the important peaks for the stability evaluation because these peaks appeared first, when the samples started to recrystallize. Peaks at 22.6, 24.1° 2θ were somewhat identical with the Gelucire 50/13 peaks[13)]

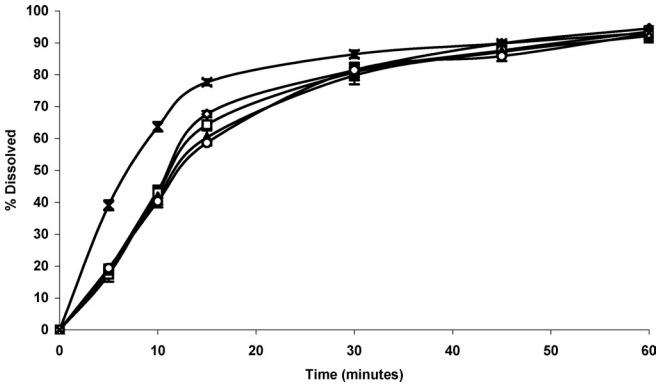

Fig. 4. *In Vitro* Dissolution Profile of MG-AET Tablet Stability Samples

Key: MG-AET (×); MG-AET tablet, initial (◇); MG-AET tablet, 10 d (□); MG-AET tablet 30 d (△); MG-AET tablet, 90 d (○).

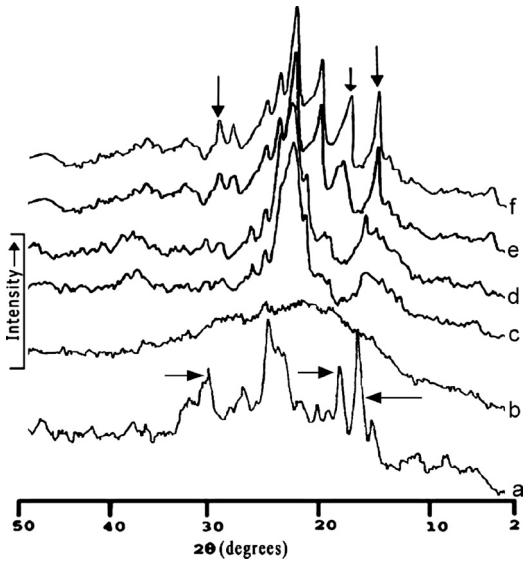

Fig. 5. XRPD Diffraction Pattern of Initial and Stability Samples of AET

Key: ET (a); AET (b); AET tablet, initial (c); AET tablet, 10 d (d); AET tablet, 1 month (e); AET tablet, 3 months (f).

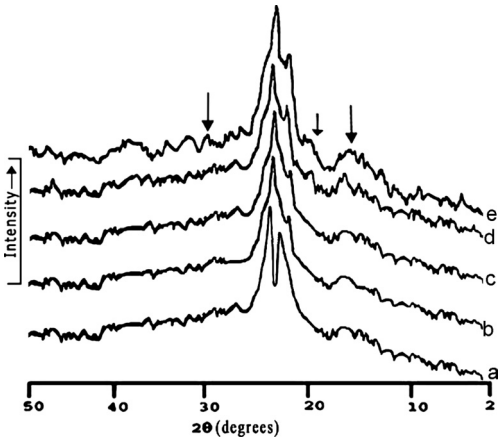

Fig. 6. XRPD Diffraction Pattern of Initial and Stability Samples of MG-AET

Key: MG-AET, initial (a); MG-AET tablet, initial (b); MG-AET tablet, 10 d (c); MG-AET tablet, 1 month (d); MG-AET tablet, 3 months (e).

and microcrystalline cellulose. The XRPD pattern of AET stability samples presented occurrence of crystallinity in the 10-d stability sample and subsequently increased. MG-AET

showed absence of ET peaks, which indicated that melt granulation did not affect the physical state of AET. Negligible increase in the peak intensity was observed in 3-month stability sample but it was insignificant to affect the dissolution. Stability on storage was attributed to the possibility of formation of hydrogen bond between the drug and lipid and immobilization of the drug in the system.[10] During compression, stabilizing effect of the Gelucire might be due to the elasticity.

Conclusion

It can be concluded that polyglycolized glycerides are able to protect amorphous etoricoxib during compression. This system gives cushioning effect to the molecules during compression and protects from transformation. On storage stability can be attributed to H-bonding phenomena and immobilization of amorphous drug in lipid matrix.

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