

EVALUATION AND ENHANCEMENT OF PHYSICAL STABILITY OF SEMI-SOLID DISPERSIONS CONTAINING PIROXICAM INTO HARD GELATIN CAPSULES

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Abstract: The aim of the study was to investigate the physical stability of the semi-solid dispersions into the hard gelatine capsules prepared with Gelucire 44/14, Labrasol and different additives such as microcrystalline cellulose (MCC), mannitol and lactose (α -monohydrate) used for enhancing the stability of the formulations. The master dispersion prepared with only Gelucire 44/14 (20% w/w) and Labrasol (80% w/w) was stored in a refrigerator ($5 \pm 3^\circ\text{C}$), while the modified dispersions with the additives (2% w/w) were kept in a climatic chamber ($25 \pm 2^\circ\text{C} / 60 \pm 5\% \text{RH}$) for 12 months. Dissolution tests of the semi-solid dispersions were performed in media with different pH's immediately after preparation and after 3, 6 and 12 months of storage. FTIR and DSC studies were also carried out at the same time points. The ideal storage condition for the master dispersion was found to be at 5°C . The addition of MCC, mannitol and lactose (α -monohydrate) to the original dispersion afforded a solidification effect on the formulation at room temperature and showed the same dissolution behavior (not less than 85% of piroxicam within 30 min in pH 1.2, 4.5 and 6.8; and water) with the master. The dispersion including lactose was stable at 25°C for 12 months. However, the ideal period of storage for the modified dispersions including MCC and mannitol was 6 months at 25°C . FTIR and DSC results both confirmed the amorphous state of piroxicam in all semi-solid dispersions under storage conditions for 12 months.

Keywords: stability, piroxicam, semi-solid dispersion, microcrystalline cellulose, mannitol, lactose (α -monohydrate), dissolution

Piroxicam is a member of the oxycam class of nonsteroidal anti-inflammatory drugs (NSAIDs) approved for acute or long-term use in the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis (1). According to the Biopharmaceutical Drug Classification System (BSC) proposed by Amidon et al. (2), piroxicam is classified as a class II compound, characterized by low solubility and high permeability. Drug dissolution *in vivo* is the rate-controlling step in drug absorption. Solid dispersions of piroxicam in water-soluble carriers, such as cyclodextrins (3), various polyethylene glycols (PEGs) (4), and Gelucire 44/14 (5, 6), are known to increase dissolution rate and bioavailability.

Gelucires with high HLB (hydrophilic-lipophilic balance) can be employed to increase the dissolution rate of drugs. Gelucire 44/14 is a semi-solid excipient of this group of Gelucires. It has a nominal melting point of 44°C and an HLB value of 14. Labrasol, with the same chemical nature as Gelucires, is a clear liquid surfactant with an HLB

value of 14. These excipients have been studied extensively for their ability to increase solubility and enhance intestinal permeability as well as the oral bioavailability of poorly water-soluble drugs (7).

Our previous study was designed to improve the dissolution rate of piroxicam at physiological pH by increasing its solubility by preparing semi-solid dispersions of the drug using Gelucire 44/14 and Labrasol (5). The original semi-solid dispersion containing a 1 : 20 ratio of drug to excipient mixture (20% Gelucire 44/14 and 80% Labrasol in w/w) demonstrated a dissolution of not less than 85% of piroxicam within 30 min in each dissolution media (simulated gastric fluid (SGF) with pH 1.2; phosphate buffers with pH's of 4.5 and 6.8; and water). An *in vivo* study measuring the bioavailability of this formulation was also performed on healthy volunteers, and the results confirmed the importance of enhancing the dissolution of the drug for increasing *in vivo* absorption (6). However, the formulation put into the hard gelation capsule was softened due to

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the high ratio of liquid Labrasol (80%) at room temperature. It is probable that the formulation inside the hard gelation capsule is thermosoftened at room temperature and may have a tendency to turn into liquid during storage and then interact with the gelatin capsule shell.

In this study, to keep the dissolution rate constant for all dissolution media in the original dispersion, different additives were added to the original formulation to solidify the dispersion at room temperature and to improve the physical stability of the dispersion under storage conditions. Modified formulations with different additives should show a similar dissolution profile to the original formulation. In this study, MCC, mannitol and lactose (α -monohydrate) were added to the original formulation to solidify it at room temperature. Microcrystalline cellulose (MCC) (8), mannitol (9) and lactose (α -monohydrate) (10) have all been added to solid dispersions as carriers to enhance the dissolution of drugs. Solid dispersions (SDs) of chlorpropamide were prepared to enhance the drugs' dissolution at two different physiological pH values, 1.1 and 7.2, simulating gastric and intestinal environments, respectively, using two grades of MCC as the carrier (8). Regarding the physicochemical properties of the piroxicam liquid solid tablets, the type of MCC used as a carrier has been investigated by Javahzadeh et al. (11). Mannitol and lactose (α -monohydrate) were investigated as carriers in preparing nifedipine solid dispersions to increase their dissolution character. In a different study, mannitol also demonstrated suitable resistance to high temperatures (9). Lactose (α -monohydrate) has been used previously as a particulate solid in dispersions, which does not dissolve or melt, but forms a dispersion in the molten excipient (10).

Interaction between drugs and excipients can alter stability of drugs. Drug excipient compatibility testing helps the evaluation of the physical stability of semi-solid dispersions during storage. The use of differential scanning calorimetry (DSC) has been proposed as a rapid method for evaluation the physico-chemical interaction between two components. However, the use of Fourier-transform infrared spectroscopy (FTIR) as complementary tool to assist in the interpretation of DSC findings is necessary (12).

In the present study, the original formulation (F1) was investigated in a 12 month stability test at $5 \pm 3^\circ\text{C}$. F1 formulation was softened due to the high ratio of liquid Labrasol (80%) at room temperature ($25 \pm 2^\circ\text{C}$). For modified semi-solid disper-

sions (F2, F3, F4), a 12 month long-term stability test at $25 \pm 2^\circ\text{C}/60 \pm 5\%$ RH (relative humidity) was performed. Original formulation (F1) and modified semi-solid dispersions (F2, F3, F4) were studied for their *in vitro* dissolution behavior immediately after preparation and after 3, 6 and 12 months of storage. Physical characterization of all the formulations was also determined by FTIR and DSC immediately after preparation and after 3, 6 and 12 months of storage.

EXPERIMENTAL

Materials

Piroxicam was obtained from Dipharma (Istanbul, Turkey), and Gelucires 44/14 (lauroyl macroglycerides) and Labrasol (caprylocaproyl macroglycerides) were supplied by Gattefosse (Saint-Priest, France). Microcrystalline cellulose (MCC) (Avicel PH-105) was obtained from the FMC (Philadelphia, USA). Mannitol (Pearlitol 300 DC) was provided by ROQUETTE (Lestrem, France), and lactose (α -monohydrate) (Granulac 200) was obtained from Meggle Ltd. (Wasserburg, Germany). Hard gelatin capsules were provided by Shionogi (Qualicaps SA, Madrid, Spain). All other chemicals used were of analytical reagent grade.

Preparation and validation of calibration curves

Stock standard solutions of piroxicam were prepared by dissolving 25 mg of drug in 100 mL of methanol. Standard solutions were prepared by dilution of the stock solutions with the phosphate buffers (pH 4.5 and pH 6.8), SGF without pepsin (pH 1.2) or water in which dissolution studies would be performed. Ultraviolet absorbance of the solutions was determined at a wavelength of maximum absorbance at 360.5 nm for pH 4.5, 354.5 nm for pH 6.8, 334.5 nm for pH 1.2, and 355.5 nm for water (Shimadzu spectrophotometer UV-1202, Tokyo, Japan).

All of the proposed methods were validated for precision (reported as the relative standard deviation, RSD %), linearity (evaluated by regression equations), detection and determination limits, and accuracy. The limit of detection (LOD) and limit of quantitation (LOQ) of the procedure (shown in Table 1), were calculated according to the $3s/m$ and $10s/m$ criteria, respectively, where s is the standard deviation of the absorbance ($n = 4$) of the sample and m is the slope of the corresponding calibration curve. The precision in RSD % was checked on the same day as well as on different days (Table 1).

Preparation of semi-solid dispersions

The calculated amounts of excipients in each formulation shown in Table 2 were weighed into a glass beaker to obtain a total mass of 20 g and heated to approximately 5°C above the melting point of Gelucire 44/14 in a water bath. The calculated amount of drug for the total mass was added to the molten vehicle with continuous stirring. Then, the mixture was poured into a plastic injector and volumetrically filled into hard gelatin capsules at the temperature close to the solidification point of the material to prevent the precipitation of the solid drug in the molten vehicle. The volumes to be put into capsules were determined through the densities of the mixtures. The weight variations of the capsules were in the range of 0.617 (4.61 as RSD %) (n = 10).

In vitro dissolution studies

Dissolution studies of the semi-solid dispersions were conducted using USP apparatus 1 (rotating basket method) (Sotax AT7 Smart, Switzerland) with three replicates, according to the USP monograph of the drug. The basket rotation speed was kept at 50 rpm. The dissolution medium was composed of 900 mL of phosphate buffers (pH 4.5 and pH 6.8), USP SGF without pepsin (pH 1.2), or water. In all experiments, 5 mL of dissolution sample was withdrawn at 5, 10, 20, 30 and 45 min and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were assayed by UV spectrophotometry. Cumulative percentages of the drug dissolved from the preparations were calculated using calibration equations.

Table 1. Statistical data for the calibration graphs of drug in different pH's.

Wavelength	pH 1.2 334.5 nm	pH 4.5 360.5 nm	pH 6.8 354.5 nm	Water 355.5 nm
Linearity range (mg/mL)	1-12.5	1.5-16	2-20	2-20
Slope ($\times 10^{-3}$)	70.3	53.2	44.2	35.9
Intercept ($\times 10^{-3}$)	3.78	5.05	-0.524	9.96
Determination coefficient (r^2)	0.999	0.999	0.999	0.999
SE of the slope ($\times 10^{-3}$)	0.280	0.153	0.118	0.235
SE of the intercept ($\times 10^{-3}$)	0.002	0.0014	0.0014	0.003
LOD (mg/mL)	0.051	0.085	0.109	0.115
LOQ (mg/mL)	0.156	0.257	0.333	0.348
Within-day precision ^a (RSD, %)	0.448	0.360	0.448	0.385
Between-day precision ^b (RSD, %)	0.921	0.754	1.30	1.09

^aEach value was obtained from six experiments on the same day. ^bEach value was determined from three different runs over 1 week.

Table 2. Formulations of semi-solid dispersions: amounts of drug and excipients in milligrams per hard gelatin capsule.

Formulation	F1	F2	F3	F4
Piroxicam	20	20	20	20
Gelucire 44/14	76	76	76	76
Labrasol	304	296	296	296
Microcrystalline cellulose	–	8	–	–
Mannitol	–	–	8	–
Lactose (α -monohydrate)	–	–	–	8

Ratio of drug/excipients: 1/20

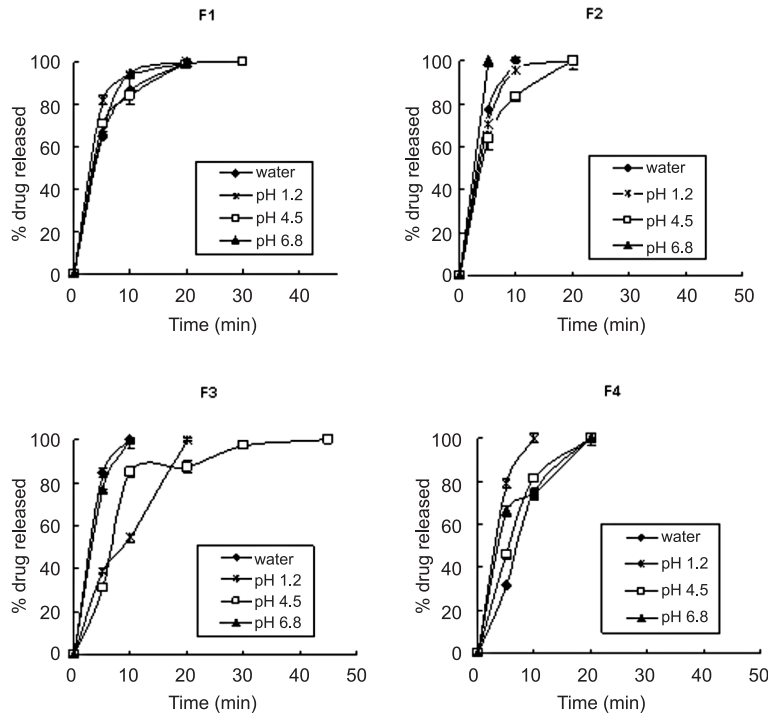


Figure 1. Dissolution profiles of drug from semi-solid formulations of F1, F2, F3 and F4 in each dissolution media (mean \pm SE, n = 3)

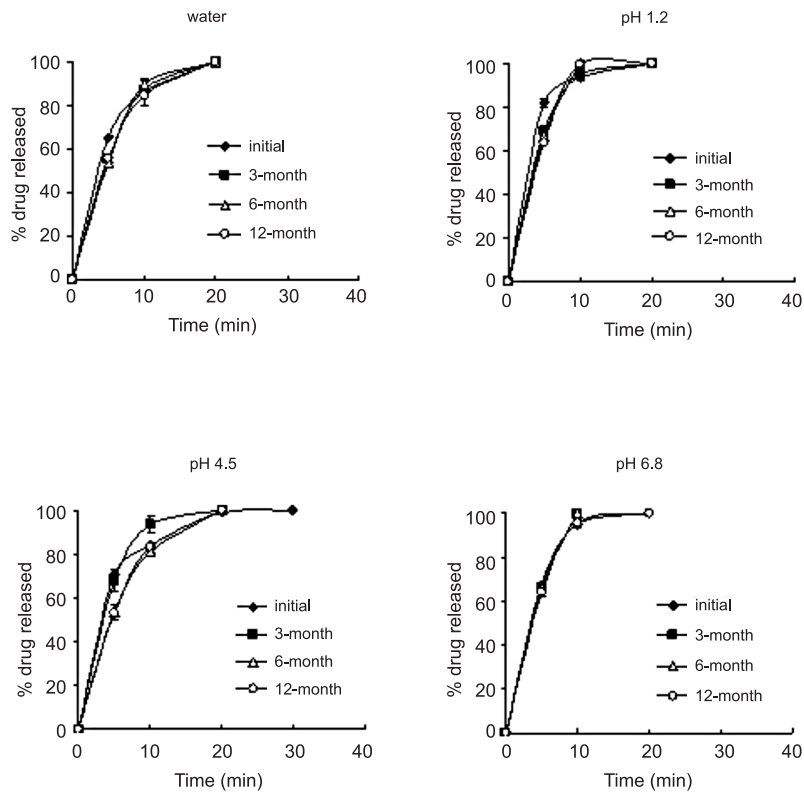


Figure 2. Effect of storage on piroxicam release from the F1 formulation in each dissolution media (mean \pm SE, n = 3)

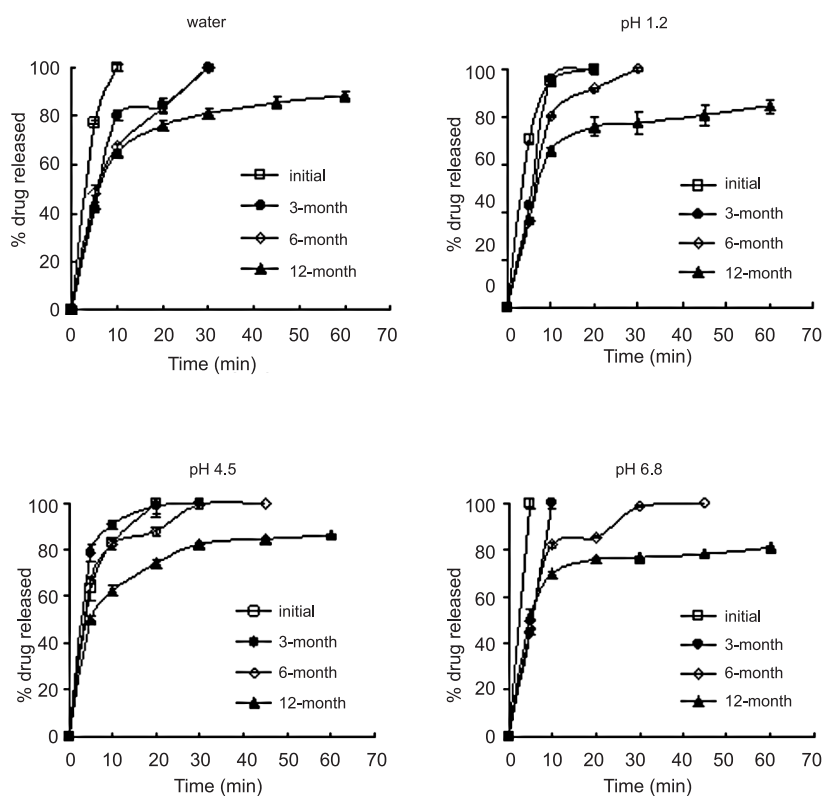


Figure 3. Effect of storage on piroxicam release from the F2 formulation in each dissolution media (mean \pm SE, n = 3)

Stability testing

Stability testing was conducted using the International Conference on Harmonization (ICH) stability conditions. Samples of the formulations were placed in closed glass vials for a period of 12 months. The F1 formulation was stored in the refrigerator ($5 \pm 3^\circ\text{C}$), and the F2, F3 and F4 formulations were kept in a climatic chamber ($25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$). The dissolution testing was conducted after 3, 6 and 12 months of storage to assess the changes in drug-release characteristics. The dissolution procedure used was as described above. The formulations were visually examined for any physical changes throughout the storage period. Observations on the physical state of the samples were also performed immediately after preparation and after 3, 6 and 12 months of storage by FTIR and DSC analyses.

Fourier transform infrared spectroscopy (FT-IR)

Drug-carrier interactions during storage conditions were determined based on IR spectra measured

by FTIR spectroscopy (Jasco, FT/IR 420). The pellets of formulation and KBr were prepared by compressing the samples at 20 psi for 5 min with KBr and the spectra were scanned over a wave number range of $4000\text{--}400 \text{ cm}^{-1}$.

Differential scanning calorimetry (DSC)

Thermal analyses were performed on the drug, excipients and semi-solid dispersions immediately after preparation and after 3, 6 and 12 months of storage using a Shimadzu DSC-60 apparatus. The thermograms were obtained by heating the samples (5 mg) at a rate of $5^\circ\text{C}/\text{min}$ from 25 to 250°C with a $5 \text{ mL}/\text{min}$ nitrogen purge.

RESULTS AND DISCUSSION

In vitro dissolution studies

A drug with low solubility but high permeability will be present in the intestine for a longer period of time, and its absorption will occur over an extended period of time. The intestinal luminal con-

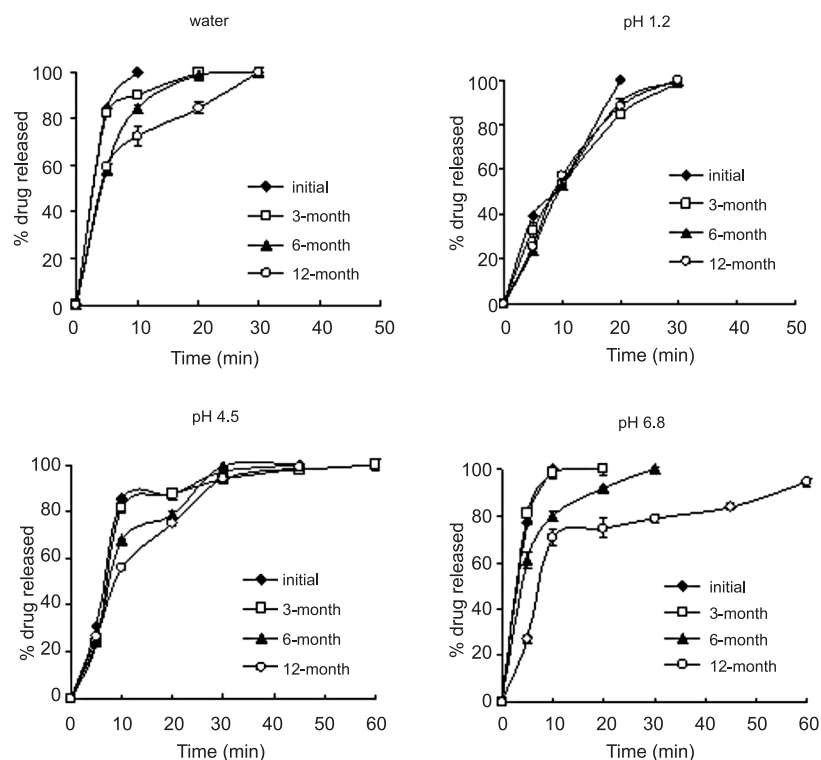


Figure 4. Effect of storage on piroxicam release from the F3 formulation in each dissolution media (mean \pm SE, $n = 3$)

tents and the intestinal membrane change along the intestine. The pH varies widely with location in the gastrointestinal tract. Consequently, the dissolution profile must be determined for at least at 4-6 time points and for at least 85% dissolution at several physiological pH's. In our previous study, we showed that the semi-solid dispersion (F1 formulation) containing a 1/20 ratio of drug to excipient mixture (20% Gelucire 44/14 and 80% Labrasol w/w) provided complete drug dissolution in all dissolution media (SGF pH 1.2, buffer pH 4.5, buffer pH 6.8 and water) within 20 min (Fig.1, F1). It was shown that the addition of MCC, mannitol and lactose (α -monohydrate) (2% in w/w) to the original formulation afforded a solidification effect at room temperature on the original dispersion. In addition, the presence of these excipients (2% w/w) in combination with Gelucire and Labrasol gave similar results in dissolution when compared to the original formulation (F1) (Fig. 1). The F2, F3, and F4 formulations (modified semi-solid dispersions) also provided at least 85% piroxicam dissolution within 30 min in each of the media immediately after preparation (Fig. 1).

Stability studies

A 12 month storage stability study was conducted on all four solid dispersion formulations. Dissolution studies were conducted on all stored samples after 3, 6 and 12 months of storage to assess any changes in the release behavior of piroxicam, compared to freshly prepared samples. Samples from the F1 formulations and the F2, F3, and F4 formulations were stored at $5 \pm 3^\circ\text{C}$ and $25 \pm 2^\circ\text{C} / 60\% \pm 5\%$ RH, respectively. Visual examinations showed that there was no change in physical appearance of the samples stored at $5 \pm 3^\circ\text{C}$ and $25 \pm 2^\circ\text{C} / 60 \pm 5\%$ in the test intervals. Figure 2 shows the effect of storage at $5 \pm 3^\circ\text{C}$ on the release of piroxicam from the original formulation (F1) over the 12-month study period. The samples of the F1 formulation kept at least 85% piroxicam dissolution within 30 min in each of the media during 12 months (Fig. 2). Thus, the ideal period of storage for this formulation could be concluded to be 12 months at $5 \pm 3^\circ\text{C}$.

Figure 3 shows the effect of storage at $25 \pm 2^\circ\text{C} / 60\% \pm 5\%$ RH on the release of piroxicam from the F2 formulation including 2% MCC over the 12-

month study period. Dissolution of the formulation did not change at the 3-month time point in all dissolution medium. At the end of 6 months of storage, the resultant decrease in dissolution was insignificant. A dramatic decrease in the extent of drug release from the formulation was observed at the 12-month time point. The percent of dissolution at 30 min was obtained as 81% in water, 78% in SGF at pH 1.2, 83% in pH 4.5 buffer and 77% in pH 6.8 buffer (Fig. 3). The F2 formulation failed to pass the dissolution limit (dissolution not less than 85% of piroxicam within 30 min in each dissolution media) at the end of 12 months of storage at room temperature, which suggests that overall the formulation was stable at 6 months.

Figure 4 shows the effect of storage at $25 \pm 2^\circ\text{C}/60 \pm 5\%$ RH on the release of piroxicam from the F3 formulation including 2% mannitol over the 12-month study period. According to the dissolution profiles, the F3 formulation exhibited the similar profiles in water, SGF pH 1.2 and pH 4.5 buffer after 3, 6 and 12 months of storage. The dissolution profiles of the formulation did not change significantly. However, at the end of 12 months of storage,

significant decrease in dissolution was obtained in pH 6.8 buffer. Seventy-eight percent of the piroxicam was released within 30 min (Fig. 4, pH 6.8). As a result, the ideal storage duration for the formulation was found to be 6 months at $25 \pm 2^\circ\text{C}/60\% \pm 5\%$ RH.

Figure 5 shows the effect of storage at $25 \pm 2^\circ\text{C}/60\% \pm 5\%$ RH on the release of piroxicam from the F4 formulation that contains 2% lactose, over the 12-month study period. At the end of 12 months of storage, the dissolution profiles of this formulation did not change in all dissolution media. As a result, it seemed that the formulation was stable in each dissolution medium under the storage conditions for 12 months.

Fourier-transform infrared spectroscopy

The subsequent phase of the study analyzed the FTIR spectra of piroxicam, Gelucire 44/14, Labrasol, MCC, mannitol, lactose (α -monohydrate) and semi-solid dispersions of F1, F2, F3, and F4 immediately after preparation and at 3, 6 and 12 months of storage. FTIR spectra are mainly used to determine whether there is a molecular change in drugs due to

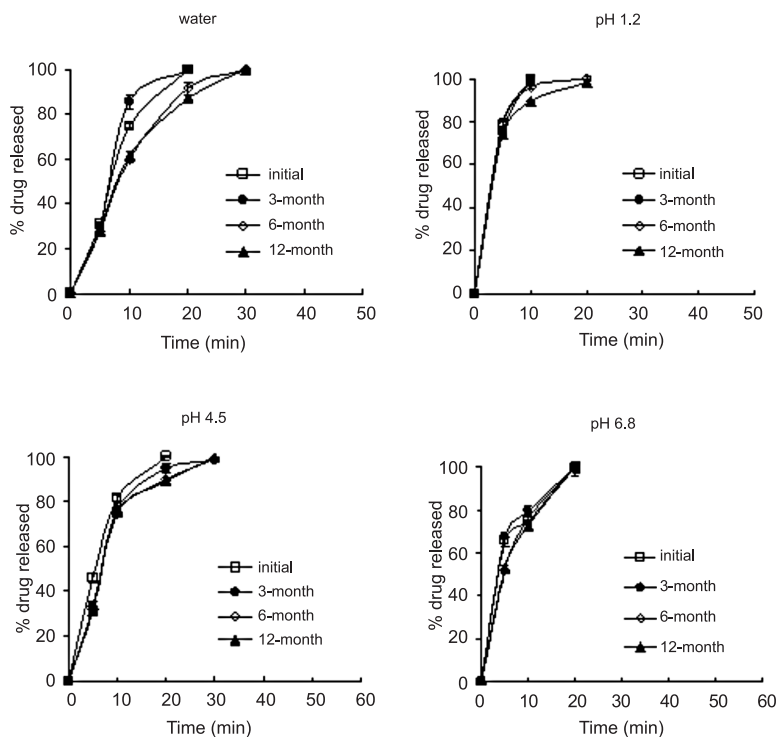


Figure 5. Effect of storage on piroxicam release from the F4 formulation in each dissolution media (mean \pm SE, $n = 3$)

interaction with its excipients or any alteration of its stability in semi-solid dispersions during storage (13). Band positions for various groups were assigned based on previous reports in the literature. Differences in the spectra with respect to band positions (in wavenumbers, cm^{-1}) in crystalline and amorphous phases of the drug were determined.

Figure 6 shows the FTIR spectra of piroxicam, Gelucire 44/14, labrasol and the formulation F1 immediately after preparation and after 3, 6 and 12 months of storage.

The main differences in the mid IR spectra of piroxicam polymorphs can be observed on bands in the range of $3300\text{--}3400\text{ cm}^{-1}$. Janik et al. (14) have found that absorption bands at 3393 cm^{-1} for form II (α , needle form) and 3341 cm^{-1} for form I (β , cubic form) represent the vibrations of the free N-H and H-bonded NH group. From the spectra of piroxicam, the peak of the N-H or O-H stretching absorption band is at 3333 cm^{-1} in form I, which is in good

agreement with the published data (15). In addition, the spectrum at 770 cm^{-1} presents a band that corresponds to an aromatic ortho-disubstituted ring. The band at 1144 cm^{-1} represents the $-\text{SO}_2\text{-N}$ functional group. The pyridine group appears at 1298 cm^{-1} . The tertiary amine group occurs at 1524 cm^{-1} . FTIR spectra of Gelucire 44/14 (Fig. 6) show characteristic peaks at 2920 and 2856 cm^{-1} (C-H stretch), 1730 cm^{-1} (C=O stretch), 1117 cm^{-1} (C-O stretching). FTIR spectra of labrasol (Fig. 6) show characteristic peaks similar to those of Gelucire because of their similar molecular structures. The spectra display broad peaks at approximately $3040\text{--}3600\text{ cm}^{-1}$, characteristic sharp peaks at 2930 and 2870 cm^{-1} (C-H stretch) and 1735 cm^{-1} (C=O stretch) and broad peaks at approximately $1200\text{--}1010$ (1110 cm^{-1}) (C-O stretching).

The peak of the N-H or O-H stretching band of piroxicam at 3333 cm^{-1} , responsible for crystalline form I, was not observed in the IR spectrum (initial)

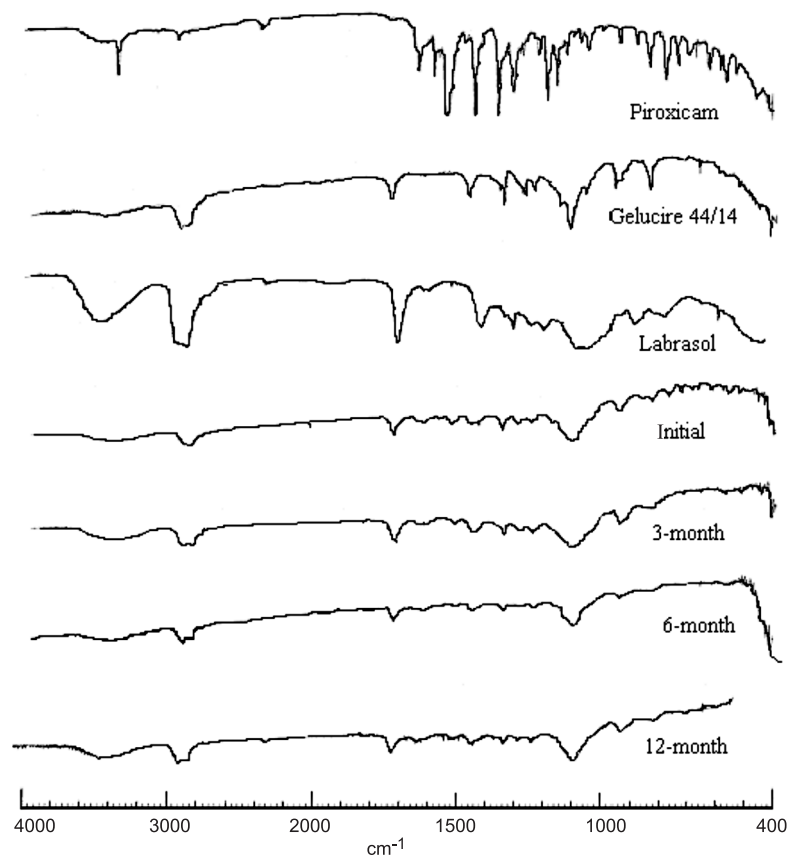


Figure 6. FTIR spectra of piroxicam, Gelucire 44/14, Labrasol, and formulation F1 immediately after preparation and after 3, 6 and 12 months of storage at $5 \pm 3^\circ\text{C}$

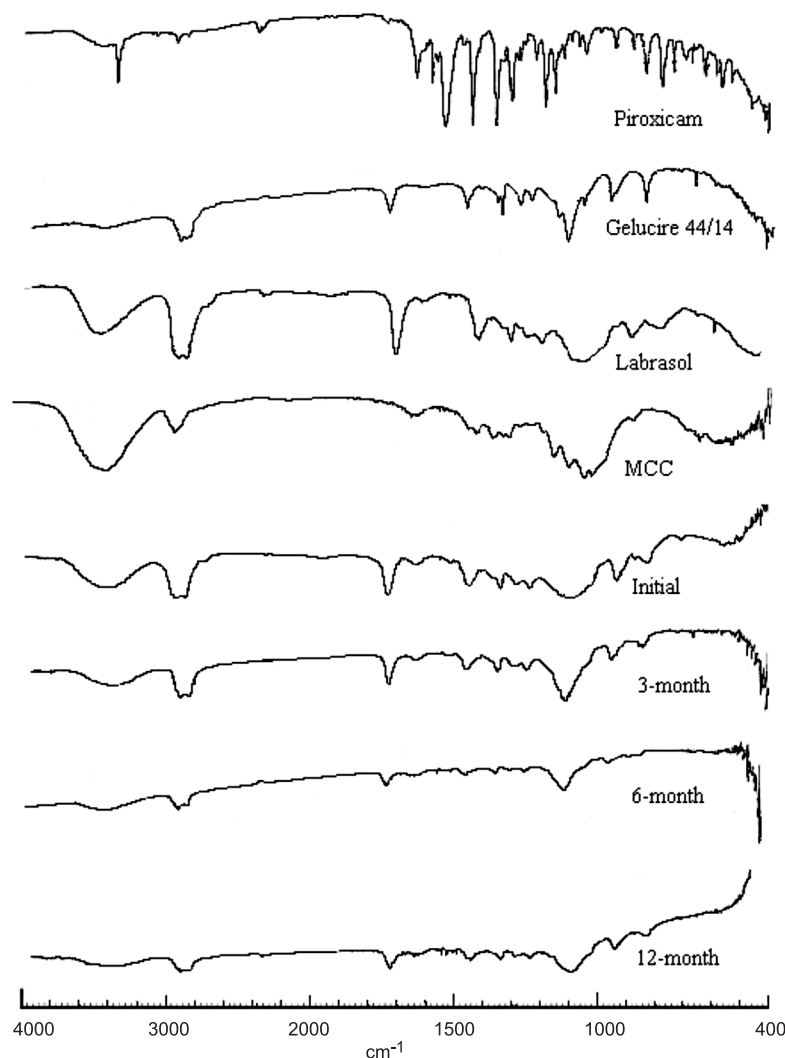


Figure 7. FTIR spectra of piroxicam, Gelucire 44/14, Labrasol, MCC and formulation F2 immediately after preparation and after 3, 6 and 12 months of storage at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$

of the F1 formulation. This indicated that form I of piroxicam converted to the amorphous state.

The shift towards a lower wavenumber for the N-H or O-H stretching vibration (at 3333 cm^{-1}) of piroxicam was attributed to a solid-state hydrogen bonding interaction between piroxicam and Gelucire 44/14 or Labrasol in the semi-solid dispersion of F1 immediately after preparation (Fig. 6). The differences in shape and position of this peak reflect the different hydrogen bonding networks in the dispersion. The intermolecular hydrogen bonding in amorphous solid dispersions may be stronger than those containing crystalline drug. Therefore,

the N-H or O-H stretching frequency may be weakened and result in a broad peak that was completely hidden by bond stretches from Labrasol. This phenomenon has also been observed previously for amorphous solid dispersion of piroxicam:PVP K30 (1 : 4) (16), piroxicam:PVP K17 (1 : 3, 1 : 4, 1 : 5, 1 : 6) and piroxicam:PVP K90 (1 : 2, 1 : 3, 1 : 4) (17).

As shown in the IR spectrum at 3, 6 and 12 months for the F1 formulation, no significant difference was observed during storage at $5 \pm 3^\circ\text{C}$ (Fig. 6).

As shown in Figure 7, FTIR spectra of the MCC exhibited the following absorption bands:

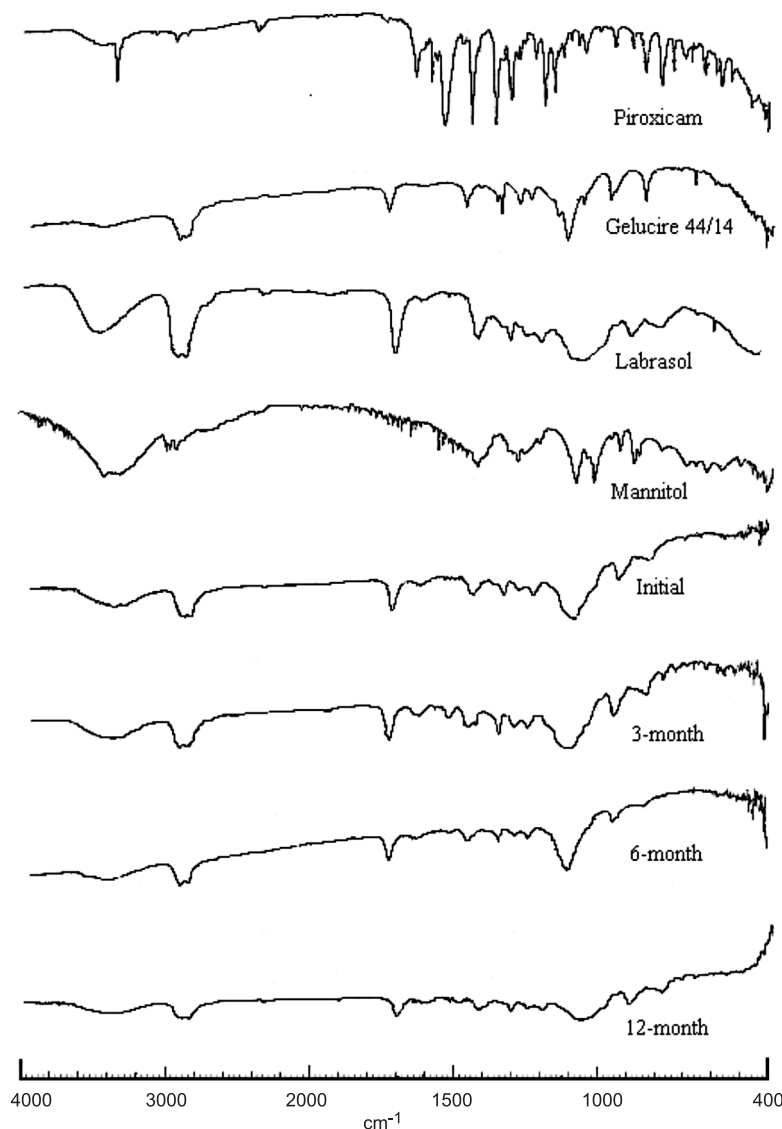


Figure 8. FTIR spectra of piroxicam, Gelucire 44/14, Labrasol, mannitol and formulation F3 immediately after preparation and after 3, 6 and 12 months of storage at 25 ± 2 °C/ $60 \pm 5\%$ RH

2870 cm^{-1} (C-H symmetric stretching), 1595 cm^{-1} (O-H symmetric stretching), and four bands between 1200-1000 cm^{-1} (C-C and C-O stretching) (18). The broad absorption in the range of 3000 to 3600 cm^{-1} can be ascribed to the stretching of H-bonded -OH groups (19). The sharp peak attributed to the N-H or O-H stretching band of piroxicam at 3333 cm^{-1} was not observed in the initial IR spectrum of the F2 formulation. This band became highly diffused and appeared as a shoulder, indicating conversion to the amorphous state. The broad peak intensity became weaker during storage. A decrease in the

band intensity in the amorphous phase was considered as an indication of weakening or strengthening of hydrogen bonding in the amorphous phase (20).

FTIR spectra for pure mannitol in 2940 and 2880 cm^{-1} represent the linking C-H and CH_2 (Fig. 8). The bands at 1400, 1280 and 1060 cm^{-1} can be attributed to the axial vibration of the C-O in the alcohol group. A very broad band is also visible at 3400 cm^{-1} , which is attributed to the presence of water (21, 22). In the formulation, the peak of asymmetric C-H vibrational stretching of mannitol between 2880 and 2940 cm^{-1} distinctively changes. This indicates that

the pure form of mannitol exists in the thermodynamically stable modification (modification I). The semi-solid dispersion preparation caused the formation of a thermodynamically less stable modification II, which is monotropically related to modification I (9).

The sharp peak of N-H or O-H stretching band of piroxicam at 3333 cm^{-1} appeared as a shoulder, indicating conversion to the amorphous state of the drug in the semi-solid dispersion (F3). The shoulder appeared with less intensity at 6 and 12 months of storage.

In Figure 9, lactose (α -monohydrate) shows a sharp medium band at 3520 cm^{-1} due to the vibration of the O-H bond of water of crystallization (23). The main band appears at 3380 cm^{-1} as a strong band ($3500\text{--}3000\text{ cm}^{-1}$) attributed to the O-H moiety. The triplet bands at 2977 , 2933 and 2900 cm^{-1} correspond to the C-H group (12).

Formulation F4, initially and after 3, 6 and 12 months of storage, demonstrated the disappearance of the peak at 3520 cm^{-1} , producing spectral evidence indicating that water was removed from crys-

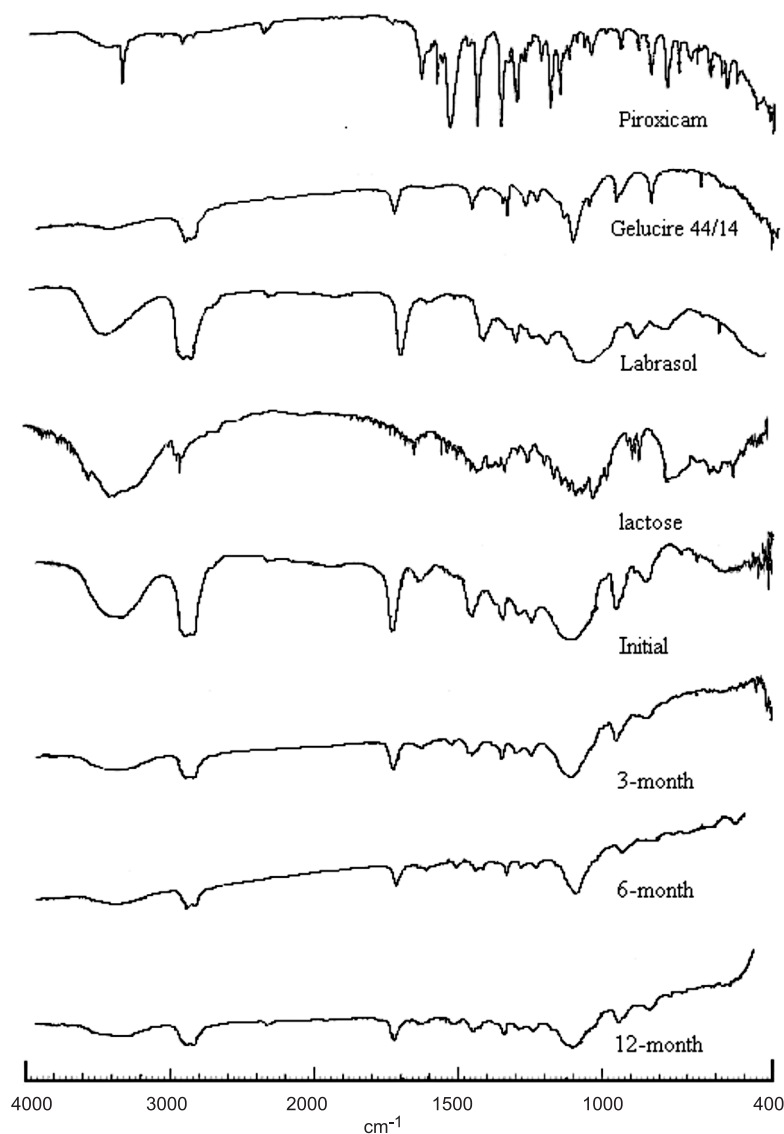


Figure 9. FTIR spectra of piroxicam, Gelucire 44/14, Labrasol, lactose (α -monohydrate) and formulation F4 immediately after preparation and after 3, 6 and 12 months of storage at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$

tal lattice. The sharp peak of N-H or O-H stretching band of piroxicam at 3333 cm^{-1} also appeared as a shoulder peak, indicating conversion to the amorphous state of the drug in the F4 semi-solid dispersion. Band intensity in the amorphous phase of drug did not change after 3, 6 or 12 months of storage.

Differential scanning calorimetry

DSC thermograms of piroxicam, Gelucire 44/14, MCC, mannitol, lactose (α -monohydrate) and semi-solid dispersions of F1, F2, F3, and F4 ini-

tially and after 3, 6 and 12 months of storage are presented in Figures 10-13. A sharp endothermic peak corresponding to the melting point of the crystalline drug was found at 201.1°C , which indicated the cubic form (β) as shown by Fernandez et al. (24). The drug also crystallizes as a needle and monohydrate (25). Studies have revealed that only modification I (cubic, β) is physically stable in the solid state upon thermolysis (26). The thermal transition of Gelucire 44/14 at 48.21°C was attributed to the melting transition of the excipient (27).

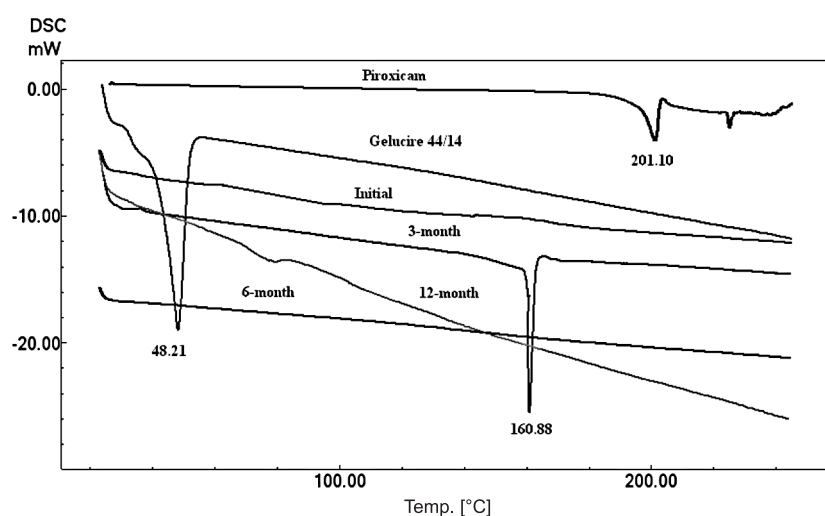


Figure 10. DSC thermograms of piroxicam, Gelucire 44/14 and F1 formulation immediately after preparation and after 3, 6 and 12 months of storage at $5 \pm 3^\circ\text{C}$

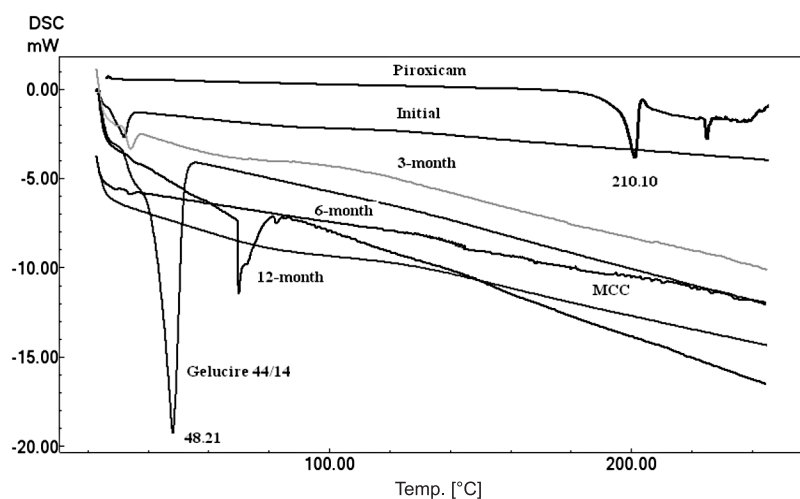


Figure 11. DSC thermograms of piroxicam, Gelucire 44/14, MCC and F2 formulation immediately after preparation and after 3, 6 and 12 months of storage at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$

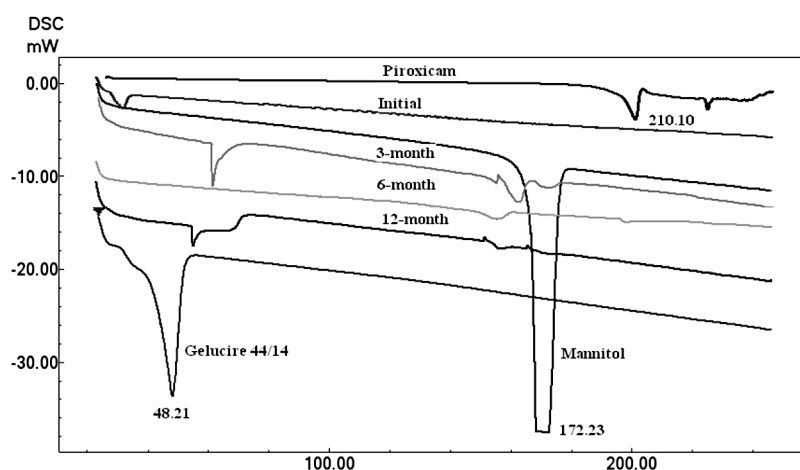


Figure 12. DSC thermograms of piroxicam, Gelucire 44/14, mannitol and F3 formulation immediately after preparation and after 3, 6 and 12 months of storage at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$

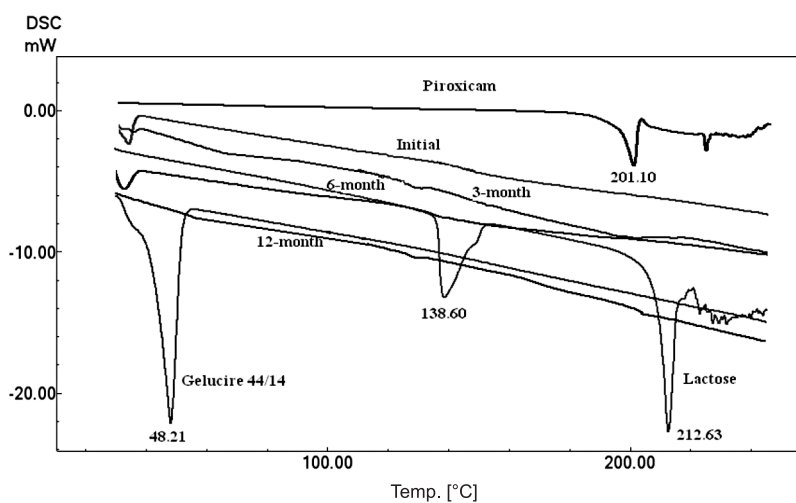


Figure 13. DSC thermograms of piroxicam, Gelucire 44/14, lactose (α -monohydrate) and F4 formulation immediately after preparation and after 3, 6 and 12 months of storage at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$.

Solid dispersions of F1 immediately after preparation and after 3, 6 and 12 months of storage produced a melting endotherm, which implies that the drug was fully amorphous during storage at $5 \pm 3^\circ\text{C}$ (Fig. 10).

An endothermic peak of MCC could be observed at approximately 200°C as reported by Bond et al. (28). However, in the DSC thermogram of MCC, no peak was observed at approximately 200°C (Fig. 11). These results suggest that the lack of an observed peak at approximately 200°C in the DSC is due to the amorphous content of MCC most-

ly residing at the surface of the sample. In the thermograms for the F2 formulation, immediately after preparation and after 3 and 6 months of storage, a peak at approximately 35°C was observed. The peak appeared with less intensity after 12 months of storage. The lowering of the endotherm is due to a decrease in the consistency of Gelucire 44/14 upon addition of Labrasol to the formulation. A sharp peak at approximately 70°C after 12 months of storage suggests a crystalline structure formation, resulting from a reaction between the -OH group on the benzothiazine ring of piroxicam and the fatty acid esters

in the excipients due to the storage conditions. No endotherm corresponding to the melting point of piroxicam was observed in the formulation thermograms immediately after preparation and after 3, 6 and 12 months of storage at $25 \pm 2^\circ\text{C}/60 \pm 5\%$ RH because the drug was completely solubilized.

Mannitol has three polymorphic forms, classified as the α , β , and δ forms. The β form was the stable form (melting peak at approximately 167°C), and the δ form was meta-stable at approximately 155°C (29). The DSC curve in Figure 12 revealed that mannitol exhibited an endothermic peak at 172.23°C , with the onset of melting at approximately 160°C . The melting peak indicated the crystalline nature of the component as received. The formulation thermograms, immediately after preparation and after 3, 6 and 12 months of storage, displayed the complete disappearance of characteristic peaks in piroxicam; therefore, it could be possible that the drug is molecularly dispersed within the solid dispersion, which undoubtedly indicates the formation of an amorphous solid solution. The peaks recorded for melting temperatures (163°C at 3 months, 155°C at 6 months and 158°C at the 12 month time point) corresponding to the fusion of mannitol, in the storage of the solid dispersion, could be explained on the basis of the crystallization of mannitol from its original form (β) to the δ variety. The sharp peaks at approximately 60°C and 53°C at the 3- and 12-month time points, respectively, suggest an unknown crystalline structure formation, which may have occurred from the reaction between piroxicam and excipients due to storage conditions.

The resultant DSC thermal curve for lactose (α -monohydrate) is shown in Figure 13. The thermal curve is characterized by a strong dehydration endothermic peak with a maximum temperature of 138.60°C . This is followed by the lactose decomposition endotherm peak at 212.63°C . The thermograms, immediately after preparation and at the 3- and 6-month time points, of the solid dispersion of F3 exhibited a shoulder at approximately 35°C corresponding to the fusion of Gelucire 44/14. In thermograms of solid dispersion, immediately after preparation and after 3, 6 and 12 months of storage, the sharp melting peak of pure piroxicam was not visible, which might be explained by the complete dissolution of piroxicam in the melted polymer. Solid dispersion with the addition of lactose (α -monohydrate) was characterized by the complete absence of any melting peaks immediately after preparation and after 3, 6 and 12 months of storage, indicating the absence of a chemical interaction between the drug and excipients.

CONCLUSIONS

It can be concluded that addition of MCC, mannitol and lactose (α -monohydrate) (2% w/w) to the original formulation afforded a solidification effect on the original dispersion initially at room temperature and after 12 months of storage. In addition, the presence of these excipients in combination with Gelucire and Labrasol demonstrated the same results in dissolution as compared to the original formulation. The ideal storage conditions for the original semi-solid dispersion were found to be 12 months at 5°C . In addition, modified semi-solid dispersions containing lactose (α -monohydrate) kept the stability at $25^\circ\text{C}/60\%$ RH for 12 months. However, the ideal period of storage for the modified dispersions including MCC and mannitol was 6 months at $25^\circ\text{C}/60\%$ RH. Additives did not exhibit significant specific chemical interactions with piroxicam in the semi-solid dispersions under storage conditions for 12 months. However, FTIR and DSC results both confirmed the amorphous state of piroxicam in all semi-solid dispersions. This state did not change significantly under storage conditions for 12 months.

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