Fig 7.1: Dissolution data of prepared Eterocoxib and commercial tablets

Fig 7.2: First order plots of prepared Etoricoxib and commercial tablets
Fig 7.3: Comparative dissolution profile of Etoricoxib from E1, E2, E3, E4 and C.T and their corresponding solid dispersions
Fig 7.4: Dissolution profile of prepared Celecoxib tablets and commercial capsule

Fig 7.5: First order plots of prepared celecoxib tablets and commercial capsules
Fig 7.6: Comparative dissolution profiles celecoxib from C1, C2, C3, C4 and C.C. and their corresponding solid mixtures
Fig 7.7: Dissolution profile of Etoricoxib tablets (E4) before and after storage at

$25 \pm 2^\circ C/60 \pm 5\% RH$

Fig 7.8: Dissolution profiles of Etoricoxib tablets E4 before and after storage at

$40 \pm 2^\circ C/75 \pm 5\% RH$
Fig 7.9: Dissolution profile of Celecoxib tables C(4) before and after storage at $25\pm2^\circ\text{C}/60\pm5\%\text{ RH}$

Fig 7.10: Dissolution profile of Celecoxib tables C(4) before and after storage at $40\pm2^\circ\text{C}/75\pm5\%\text{ RH}$
Results and discussion for Etoricoxib and Celecoxib:

Tablets of Etoricoxib and Celecoxib solid mixtures were compressed by wet granulation using lactos and PVP in alcohol, cross caramelllose sodium was used as disintegrant.

7.5. Results and discussion for Etoricoxib:

7.5.1. Uniformity of weight, hardness, friability, disintegration time and drug content:

To evaluate the effectiveness of the solid mixtures of Etoricoxib, tablets of Etoricoxib were formulated and studied. The quality control tests such as uniformity of weight, hardness, friability, disintegration time and drug content for all the prepared formulations were performed and the results are given in Table 7.2. All the formulations complied with compendial standards for uniformity of weight (not more than two of the individual weights deviate from the average weight by more than 7.5% and none deviates by more than twice that). The hardness for all the formulations was found to be in the range of 4–5 Kg/cm² and was satisfactory. The percentage weight loss in the friability test was found to be less than 1% for the batch of tablets. All the tablets prepared by wet granulation method fulfilled the compendial requirement of disintegration time except formulation (E1), compressed with pure Etoricoxib (<15 min). The drug content of the tablets when assayed spectrophotometrically was found be 100 ± 2 %. Low s.d. values in drug content ensured uniformity of drug in the prepared formulations.
7.5.2. In vitro dissolution studies:

All the tablet formulations and commercial Etoricoxib tablet were subjected to in vitro dissolution studies and are shown in Table 7.3 and Fig. 7.1 respectively. The Etoricoxib released from formulation E1 is 66.65% in 60 min, E2 released 92.19% in 60 min, E3 released 94.90% in 60 min, E4 released 99.40% in 40 min and CT released 99.88% in 60 min. The \( \text{DE}_{10} \) and \( \text{DE}_{20} \) values and \( T_{50} \) and \( T_{90} \) values are shown in Table 7.4. The \( \text{DE}_{10} \) value of formulation E1 is 10.18, E2 is 21.80, E3 is 24.37, E4 is 30.95 and CT is 28.46. The \( \text{DE}_{10} \) value of formulation E4 is higher compared to all other tablet formulations. The \( T_{50} \) values of formulation E1 are 38.1, E2 is 14.8, E3 is 12.2, E4 is 10.0 and CT is 11.1 min respectively. Over all the order of drug release from the formulations prepared by both methods and commercial tablet are in the order of E4 > CT > E3 > E2 > E1 (based on the dissolution parameters).

7.5.3. Drug release kinetics:

The release profiles of Etoricoxib from the tablets were fitted to different release kinetics, such as zero order, first order and Hixson-Crowell cube root models. The values of correlation coefficient (r), rate constants for zero order, first order and Hixson-Crowell cube root model are given in Table 7.5 & 7.6 respectively. The log% drug remaining to be dissolved vs. time plot was drawn and shown in Fig. 7.2. The dissolution of Etoricoxib from all the tablet formulations followed first order release with correlation coefficient (r) values ranging from 0.9612 to 0.9959. The first order release rate constant (\( k_1 \)) values of tablet formulation E1 are 0.0186, E2 is 0.0386, E3 is 0.0467, E4 is 0.0937 and CT is...
0.0541 respectively. Formulation E4 exhibited higher $k_1$ value compared to all other formulations prepared by both methods wet granulation and direct compression. The $k_1$ values from these tablets followed the order of E4>CT>E3>E2>E1. The drug release followed erosion mechanism for all the prepared tablets in the similar lines with that of the solid mixtures. The release of the drug from the commercial tablet also followed erosion.

7.5.4. Comparison of the dissolution profiles of the solid mixtures and corresponding tablets:

A comparison of the dissolution profiles of the solid mixtures and tablets prepared with the corresponding solid mixtures were given in the Fig. 7.3. The release of drug from these prepared tablets is slower when compared to solid mixtures, this might be due to the compaction force acting on these tablets and time required for these tablets to disintegrate and dissolve. Thus the Etoricoxib-PVP K30 solid mixtures are useful in developing suitable tablet formulations of Etoricoxib though there is a delay in the drug release compared to solid mixtures it gave faster release compared to commercial tablet formulation.

7.6. Result and discussion for Celecoxib:

Celecoxib solid mixture compressed into tablet by using wet granulation technique. Direct compression technique was not attempted due to more bulk of the tablet

7.6.1. Uniformity of weight, hardness, friability, disintegration time and drug content:
The prepared tablets of the Celecoxib solid mixtures complied with compendial standard for uniformity of weight (not more than two of the individual weights deviate from the average weight by more than 5% and none deviates by more than twice that). The hardness was found to be in the range of 4–5 Kg/cm² and no significant loss in the friability (less than 1%). Except the formulation C1 prepared with pure drug all other tablets fulfilled the official requirement of disintegration time (<15 min). The drug content of the tablets was found be 100 ± 2 %. Low c.v. values in drug content ensured uniformity of drug in the prepared formulations. The results are shown in Table 7.8.

7.6.2. In vitro dissolution studies:

In vitro dissolution profiles of Celecoxib tablets prepared with different solid mixtures and commercial Celecoxib capsule are shown in Table 7.9 and Fig.7.4 respectively. The formulation C1 released 92.79% drug in 60 min, C2 released 98.45% drug in 60 min, C3 gave 99.54% drug release in 60 min, C4 gave 99.80% drug release in 45 min and CC released 99.04% drug in 45 min.

The DE₁₀ and DE₂₀ values and T₅₀ and T₉₀ values are shown in Table 7.10. The DE₁₀ value of formulation C1 is 18.87, C2 is 27.96, C3 is 28.56, C4 is 29.55 and CC is 28.60. The DE₁₀ value of formulation C4 is higher compared to all other tablet formulations. The T₅₀ values of formulation C1 are 14.9, C2 is 11.3, C3 is 7.30, C4 is 7 and CC is 8 min respectively. The other dissolution parameters were also in the same order. Over all the order of drug release from the formulations prepared by wet granulation method and commercial capsule are in the order of C4>CC>C3>C2>C1.
7.6.3. Drug release kinetics:

The dissolution date of the prepared Celecoxib tablets and commercial capsule was fitted to zero order, first order and Hixson-Crowell cube root models. The respective correlation coefficients (r) and rate constants are given in Table 7.11 & 7.12 respectively and the first order plots are shown in Fig. 7.5. The drug release followed first order for both the prepared tablets and commercial capsule (first order correlation coefficient (r) values ranging from 0.9768 to 0.9976). The first order release rate constant value (k1) of tablet formulation C1 is 0.0124, C2 is 0.0644, C3 is 0.0724, C4 is 0.0824 and CC is 0.0727 respectively. Formulation C4 exhibited higher k1 value compared to all other formulations prepared by wet granulation method (C4>CC>C3>C2>C1).

7.6.4. Comparison of the dissolution profiles of the solid mixtures and corresponding tablets:

A comparison of the dissolution profiles of the solid mixtures and tablets prepared with the corresponding solid mixtures were given in the Fig. 7.6. Slower drug release was observed from the tablets compared to their respective solid mixtures. The reason could be the compression force and time required for the release of drug from the disintegrated granules. The superiority of solid mixture CXB: PVP K30 -1:6-SE was proved in the tablet formulation also in releasing the drug at a faster rate compared to other tablets though the rate is slower compared to the solid mixture. This formulation could release the drug at faster rate compared to the commercial capsule and hence it could be a better choice.
7.7. Stability studies of the promising formulations:

In pharmaceutical sense, stability is technically defined as capability of a particular formulation, in a specific container closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological classification during the assigned shelf life. Stability studies on a new drug per se and the formulations containing it are an integral part of its development program.

An ideal release dosage form apart from other requirements should provide consistency of drug release throughout its shelf life. In the present investigation stability studies were performed on the following experimental formulations.

1. Etoricoxib tablets (E4)
2. Celecoxib tablets (C4)

7.7.1. Procedure:

In each case all formulations were packed in HDPE screw caped bottles and kept in humidity chambers maintained at 25±2°C/60±5%RH and 40±2°C/75±5%RH as per ICH guidelines for Zone III. The samples were also subjected to intermediate condition of 30±2°C/65±5%RH. In each case the samples stored in 25±2°C/60±5%RH storage conditions were withdrawn after 3 and 6 months and in the case of samples stored in 40±2°C/75±5%RH storage conditions were withdrawn at 1, 2, 3 and 6 months. These samples were analyzed for appearance, hardness, assay or drug content and in vitro dissolution performance. The results are shown in the accelerated stability data Table 7.13.
& 7.15 for E4 & C4 tablets respectively. Comparative dissolution profiles with the initial sample were shown in Table 7.14 & 7.16 for E4 and C4 tablets respectively.

7.8. Results and discussion of Stability Studies:

No visible physical changes were observed in all the formulations withdrawn from the humidity chambers. The average weight, hardness and drug content in all the formulations were found to be satisfactory and given in Table 7.13 & 7.15 for E4 and C4 respectively. The dissolution profiles of the Etoricoxib and Celecoxib before and after storage are given in Table 7.14 & 7.16. The drug release profiles of all the formulations did not change significantly after storage at 25±2°C/60±5%RH and 40±2°C/75±5%RH for a period of six months (Fig. 7.7 & 7.8 for E4 and Fig. 7.9 & 7.10 for C4). The release of the Etoricoxib and Celecoxib remained unaltered. As the tested experimental products showed positive results in the accelerated storage conditions of 40±2°C/75±5%RH, the samples collected at different time intervals from the intermediate storage conditions 30±2°C/65±5%RH were not analyzed as per ICH guidelines.

Hence from the stability studies it could be concluded that all the experimental formulations of Etoricoxib and Celecoxib are stable as per ICH guidelines.
REFERENCES


