Instability of misoprostol tablets stored outside the blister: a potential serious concern for clinical outcome in medical abortion

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Context

- Misoprostol (brand name Cytotec®) is routinely used for medical termination of pregnancy at 200 to 800µg single dose.
- Misoprostol tablets are most often packaged as multiple (10) tablets within an aluminium strip, each within an individual alveolus. Therefore, the blister has to be cut to provide the patient with the appropriate dose.
- When an alveolus is opened, tablets will be exposed to atmospheric conditions.

Objective

- The aim of this research was to study the changes in the stability of misoprostol (Cytotec®, Pfizer) associated with exposure of the tablet to typical European air/humidity conditions, such as might be the case with inadvertent opening of the alveoli.

Material and Methods

- 8 commercial boxes of 60 Cytotec tablets were used
  - 60 tablets stored in non damaged blisters, named T0= reference
  - 7 boxes of 60 tablets taken out of their blister and stored in a climatic chamber (WTB BINDER GmbH) at 25°C/60%RH (median usual European conditions to be used for stability studies according to EMA) each for 1 hour; 6 hours; 1 day; 2 days; 7 days; 15 days; 30 days
- Tablets water content, pharmaco-technical characteristics- i.e. weight, thickness and diameter- and composition in misoprostol and decomposition products were compared between the samples of tablets exposed to environmental conditions for different durations and reference tablets (T0).

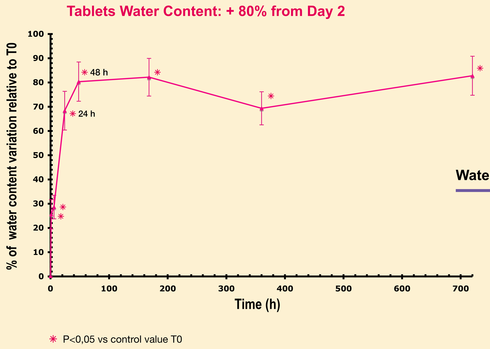
Pharmacotechnical methods
according European Pharmacopea
- Mass uniformity
- Friability
- Hardness
- Diameter and thickness of tablets

Water content
Karl Fisher Metrohm: 787 KF Titrino

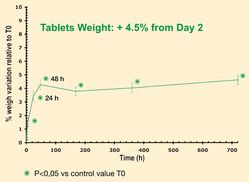
Analytical studies
HPLC LaChrom Elite VWR 13
- Misoprostol dosage
- Decomposition products dosage: type A, type B and 8 epi misoprostol

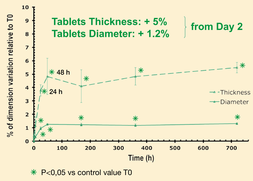
= non active products

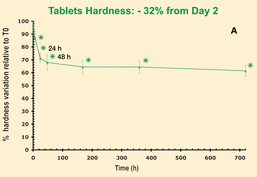
Results

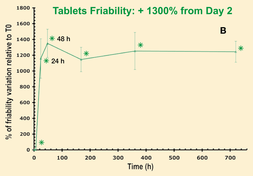


Water Penetration

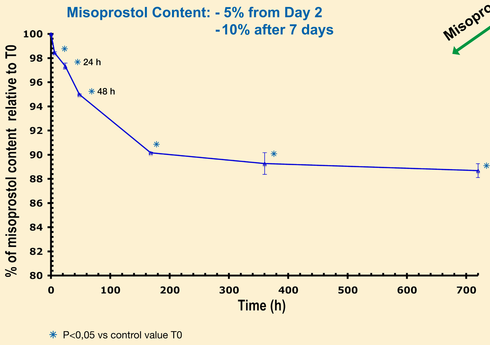


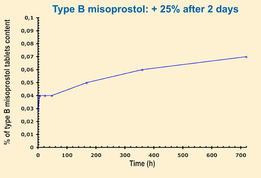


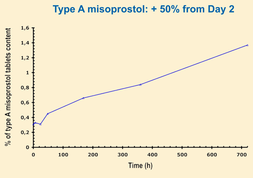


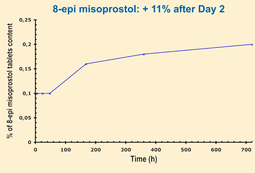


Misoprostol Degradation









Non active products obtained by dehydratation and/or isomerisation of misoprostol

Discussion and Conclusion

- Any change above 10% for tablets characteristics, i.e. diameter, thickness, resistance, and weight leads to data outside the range described by the European Pharmacopeia and therefore to non-conform tablets.
- Following exposure of misoprostol to atmospheric conditions, a significant increase in tablet water content was associated with a significant increase in tablet friability from Day 2 and with a significant decrease in active ingredient: 5% from Day 2 and 10% by the end of one week.
- A reduction in clinical effectiveness is a real possibility following exposure of misoprostol to atmospheric conditions.

Special caution must be taken in storing and delivering misoprostol tablets.