Objectives

1. Design a 24 hour zero order release tablet containing a freely soluble basic drug (H131)
2. Investigate the effect of anionic polymers and hydroxypropyl methylcellulose (HPMC) on drug release rate
3. Evaluate the different manufacturing processes on drug dissolution profile

Background

The extended-release (ER) products of highly water soluble drugs are commonly formulated as osmotic pump, bilayer/layers tablets, multiple-pulse microencapsulation, matrix tablets with functional coating or matrix tablets using gastric retention technology. It is difficult to achieve up to 24 hour for matrix tablets composed ofcontrolled release core containing polymers. Recently, the approach of ion interaction 14 between basic drugs and anionic polymers along with a blend of non-ionic polymers achieved extended release. H131, a highly water soluble basic drug was designed, to be one-day matrix tablets with up to 24 hour drug release (>90% at 24 hour) with a good linear release (R2=0.95) by its interaction with anionic polymers, such as Eudragit L100-55 & Carbopol 934P.

Materials

H131 (Zhejiang, China), Hydroxypropyl methylcellulose - Methocel ® K100 LV, K4M, K15M, K100M (The Dow Chemical Company), Lactose (DMV-Förrântor, Gluconolactone - Compritol ® 888 ATO (Gattefosse), Sodium alginate - Avicel, 200 Pharma (Eironix), Methacrylic Acid Copolymer, Type C - Eudragit ® L 100,55 and Eudragit L 30 D-55 (Eironix), Carbomer Homopolymer Type A - Carbopol ® 791P NF (Lutriette), Magnesium stearate (Malinkor).

Methods

GRANULATION

Wet granulation - H131 mixed with fillers and anionic polymers, such as Eudragit ® L 100-55 or Carbopol 934P. Add water, Eudragit ® L 10 D-35 or isopropanol alcohol to conduct wet granulations.

Hot - melt granulation - H131 mixed with filler and Compritol /888 ATO. Heat the mixture to about 70% and then add and get granulation after the melt had cooled down.

Dry granulation - H131 mixed with fillers, anionic polymers, such as Eudragit ® L 100-55 and magnesium stearate. Dry granulation was obtained from a roller compactor.

All the granulations were passed through a 20 mesh screen.

BLENDDING

Blend the above granules with HPMC, filler and colloidal silicon dioxide for 10 min, then add magnesium stearate and blend for another 3 min. For direct compression, mix the weighed materials, except for magnesium stearate, for 3 min; pass through a 20 mesh screen and blend for 10 min. Add magnesium stearate, pass through a 30 mesh screen, and blend for 5 min.

COMPRESSION

The blends were compressed into round tablets with weight around 350mg and hardness approximately 4Kp.

RESULTS AND DISCUSSION

H131 is a freely soluble, weak basic drug. Interestingly, HPMC alone or HPMC/wax blend cannot effectively control the drug release up to 24 hours with as high as 80% Methocel ® K100M in the matrix tablets, and only first order release profile was observed. When the drug formulated with anionic polymer Eudragit ® L100-55 and Methocel ® K100M, the drug release can be controlled up to 24 hours (Fig 1).

Conclusions

• Neutral polymer and/or wax alone failed to control H131 release for up to 24 hours from matrix tablets due to APH high solubility and low dye.
• Anionic polymers, such as Eudragit ® L100-55 and Carbopol 934P, could interact with H131 at neutral and high pH environments. The combination of anionic polymers and HPMC can retard H131 release from matrix tablets.
• The approach applied drug-anionic polymer interaction to prolong drug release up to 24 hours with near zero order release was successfully demonstrated.
• The manufacturing processes have a significant effect on drug release.

References

2. Takka E, Farmaco, 58(2003):1051-1056