Ionic Interaction to Achieve 24 Hour Zero Order Release for a Freely Soluble Drug

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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/trilayer tablets, multi-pulse microparticles, matrix tablet with functional coating or matrix tablets using gastric retention technology. It is difficult to achieve up to 24 hour release for matrix tablets composed of common release controlling non-ionic polymers. Recently, the approach of ionic interaction[1-4] between basic drugs and anionic polymers along with a blend of non-ionic polymers achieved extended release. H131, a very high water soluble basic model drug with a low dose, was designed to be once-a-day matrix tablets with up to 24 hour drug release (>90% at 24 hour) with a good linear release (R^2>0.95) by its ionic interaction with anionic polymers, such as Eudragit® L100-55 & Carbopol® 971P.

Materials

H131 (Zhejiang, China), Hydroxypropyl methylcellulose - Methocel® K100 LV, K4M, K15M, K100M (The Dow Chemical Company), Lactose Monohydrate (DMV-Fonterra), Glyceryl Behenate - Compritol® 888 ATO (Gattefosse), Colloidal silicon dioxide - Aerosil® 200 Pharma (Evonik), Methacrylic Acid Copolymer, Type C - Eudragit® L 100-55 and Eudragit L 30 D-55 (Evonik), Carbomer Homopolymer Type A - Carbopol® 971P NF (Lubrizol), Magnesium stearate (Mallinckrodt).

Methods

GRANULATION

Wet granulation – H131 mixed with filler and anionic polymers, such as Eudragit® L 100-55 or Carbopol® 971P. Add water, Eudragit® L 30 D-55 or isopropyl alcohol to conduct wet granulations.

Hot – melt granulation - H131 mixed with filler and Compritol® 888 ATO. Heat the mixture to about 70ºC under mixing and get granulation after the mixture cool down to room temperature.

Dry granulation – H131 mixed with filler, 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

BLENDING

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 5 min, pass through a 20 mesh screen and then blend for 10 min. Add magnesium stearate, passed through a 30 mesh screen, and blend for 3 min.

COMPRESSION

The above blends were compressed into round tablets with weight around 350mg and hardness approximately 8Kp.

DISSOLUTION TEST

The release of H131 from matrix tablets was analyzed by a HPLC method with UV detector using USP apparatus I at 100rpm in pH 6.8 phosphate buffer.

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 tablet, 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).

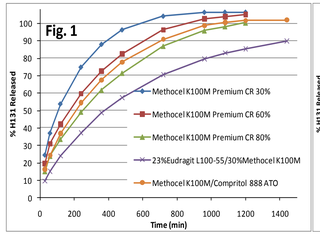

Fig. 1: Dissolution of H131 ER Tablets containing various polymers.

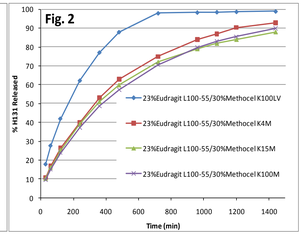

Fig. 2: Effect of HPMC on release of H131 ER tablets containing Eudragit® L100-55.

HPMC (30%) grades don't show a significant effect on dissolution of the formulations containing 23%w/w Eudragit® L100-55 once their viscosity grades reach Methocel® K4M or higher (Fig. 2)

Drug release decreased with the increase of Eudragit® L100-55 from 23%w/w to 46%w/w for H131 ER tablets containing 30% Methocel K15M or blends of 15% Methocel® K100LV and 15% Methocel® K15M. The HPMC blends give a better linearity than Methocel® K15M alone, especially, for the formulation containing a high amount of Eudragit® L100-55 (Fig. 3 and Table 1).

H131 ER tablets were manufactured by three different methods, wet granulation, dry granulation and direct compression. The manufacturing processes have a significant effect on drug release profiles. The dissolution results indicate that wet granulation has the slowest release profile, and direct compression shows the quickest drug release rate (Fig. 4).

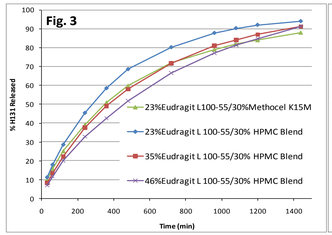

Fig. 3: Effect of Eudragit® L100-55 on the dissolution of H131 ER tablets.

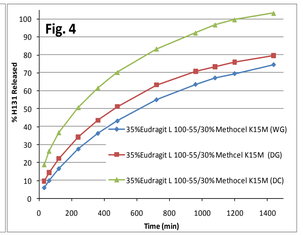

Fig. 4: Dissolution of H131 ER tablets made by different granulation methods.

Carbopol® 971P NF is another anionic polymeric excipient that is often used in extended release formulations. It has the synergistic effect when it is formulated together with HPMC. The dissolution profiles become slower when more Carbopol® 971P is used in the formulations (Fig 5).

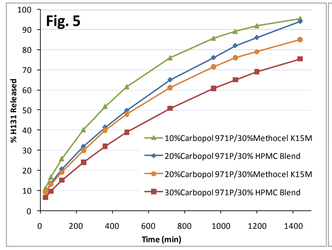

Fig. 5. Dissolution of H131 ER tablets containing different amount of Carbopol® 971P.

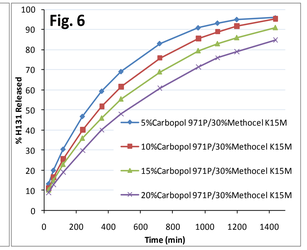

Fig. 6: Dissolution of H131 ER tablets containing Carbopol® 971P and HPMC.

H131 ER formulations containing HPMC blend of 15% Methocel® K15M and 15% Methocel® K100LV showed better linearity. The R^2 is higher than 0.97 for H131 ER tablets composed of 30% HPMC blend and 20% or 30% Carbopol® 971P (Fig. 6 and Table 1).

Table 1: Linearity of H131 release profiles from anionic polymeric matrix tablets

Anionic Polymers	Formulations	R^2
Eudragit® L100-55 Formulations (Fig. 3)	23%Eudragit® L100-55/30%Methocel® K15M	0.8707
	23%Eudragit® L 100-55/30% HPMC Blend	0.8998
	35%Eudragit® L 100-55/30% HPMC Blend	0.9248
	46%Eudragit® L 100-55/30% HPMC Blend	0.9522
Carbopol® 971P Formulations (Fig. 6)	10%Carbopol® 971P/30%Methocel® K15M	0.9212
	20%Carbopol® 971P/30%Methocel® K15M	0.9601
	20%Carbopol® 971P/30% HPMC Blend	0.9711
	30%Carbopol® 971P/30% HPMC Blend	0.9747

For weakly basic drug verapamil HCl, Eudragit® L100-55 resulted in release retardation due to an interaction between the anionic polymer and the cationic drug. The ionic interaction was characterized by NIR, FT-IR, and MTDSC techniques. Drug release decreased with an increase of Eudragit® L100-55 levels[1]. The interaction between propranolol HCl and methacrylic acid copolymers was evaluated [2]. Hydrogen bonding was identified between drug and the anionic polymers, and the pH conditions can influence this binding. The drug release was controlled with the type of anionic polymer and the interaction between propranolol HCl and anionic polymers [3].

Interaction of the tertiary amine nitrogen of verapamil hydrochloride with the anionic carboxyl group on Carbopol 934P, forming an insoluble complex, reduced the rate of drug release [4].

Anionic polymers, Eudragit® L100-55 and Carbopol® 971P NF, can effectively control the release of H131. Carbopol® 971P NF, a lightly crosslinked polymer with long rheology, is more efficient in controlling drug release than Eudragit® L100-55, a linear polymer that can dissolve at pH about 5.5. Besides H131-anionic polymer interaction, Carbopol® 971P NF polymer is slightly crosslinked and provides a three dimensional gel structure which is more resistant to diffusion and erosion than Eudragit® L100-55.

Conclusions

- Neutral polymer and/or wax alone failed to control H131 release for up to 24 hours from matrix tablets due to API's high water solubility and low dose.
- Anionic polymers, such as Eudragit® L100-55 and Carbopol® 971P, 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

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