

EXTENDED RELEASE (ER) FORMULATIONS OF A PRACTICALLY INSOLUBLE MACROLIDE ANTIBIOTIC CLARITHROMYCIN

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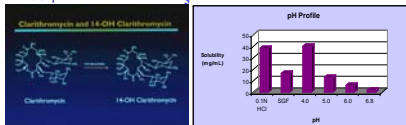


ABSTRACT

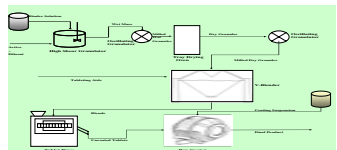
Purpose. To develop ER formulations of a practically insoluble macrolide antibiotic suitable for once-a-day oral administration. **Methods.** Clarithromycin is a broad-spectrum macrolide antibiotic, generally administered *qd* for two 500 mg tablets. Six tablet formulations all containing 500 mg drug, each utilizing different rate-controlling polymers were initially developed. The polymers investigated include carboxypol* 71G, low-viscosity (LV) hypromellose, polyox* 750N, hypromellose K4M* as well as LV-ethylcellulose (EC) interspersed with pore-formers like Kluccel®, LF and LV-hypromellose. A novel 1000 mg formulation of clarithromycin containing no dissolution-controlling polymer was subsequently devised. The formulation comprised of drug granulated and tableted with commonly employed tableting aids like MCC, talc, lactose, colloidal silicon dioxide and magnesium stearate. The effect of different LV conventional binders for granulation such as PVP, HPC and HPMC on the tableting characteristics of this erosion-based tablet matrix was studied. The effect of presence of an inorganic acid like HCl on the *in vivo* absorption of drug in the fed-state was investigated. **Results.** While approximately 7%-15% w/w each of carboxypol®, LV-hypromellose and polyox* in the formulation resulted in release profiles that were comparable to the brand product, greater than 50% w/w combination of both EC-HPC and EC-HPMC was required in order to obtain comparable release. Tablets containing less than 4% hypromellose K4M* were found to have better stability at 40°C/75%RH than those with carboxypol 71G*. Similarly, the EC-HPC formulation was comparatively more stable than the EC-HPMC tablets. Tablet dosage forms without any rate-controlling polymers exhibited a near zero-order drug release when tested in 0.1 M Na acetate buffer at pH 5.0. HPMC was proven to be the best wet-granulation binder for this particular formulation. Plasma drug concentration profiles of formulations with and without HCl were similar. **Conclusions.** A broad range of extended-release tablet matrices of clarithromycin can be developed with and without the use of any rate-controlling polymers.

INTRODUCTION

- Clarithromycin is a broad-spectrum semi-synthetic macrolide antibiotic used against a wide variety of gram-positive and gram-negative pathogens. It is indicated for the treatment of a wide variety of respiratory and dermatological infections in children and adults¹.
- It is a white to off-white crystalline, odorless powder with a bitter metallic taste. It is practically insoluble in water and slightly soluble in alcohol and methanol².
- It is rapidly absorbed from the GI tract and undergoes first-pass metabolism to 14-OH clarithromycin. The anti-microbial activity of the metabolite is superior to that of the parent compound³.
- Clarithromycin exhibits pH-dependent solubility. The solubility decreases with increase in the GI pH.



PROCESS FLOW DIAGRAM



OBJECTIVES

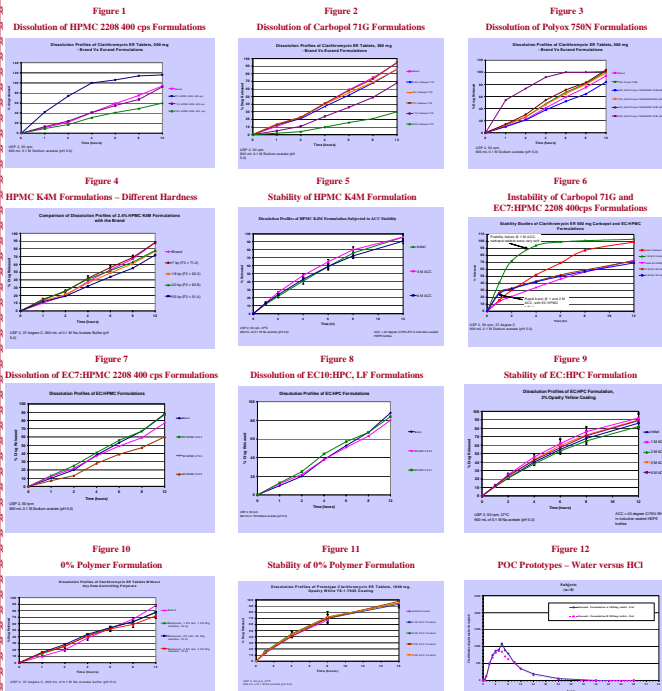
- To develop extended release tablet formulations of Clarithromycin suitable for once-a-day (*qd*) administration in humans, either as two 500 mg tablets or a single 1000 mg tablet comparable in shape and size to the prescribed brand product.
- To formulate the said 500 mg tablets utilizing either approximately no more than 4% or no less than 50% of a combination of different pharmaceutically acceptable polymers.
- To formulate the said 1000 mg tablet without the use of any dissolution rate-controlling agent, a polymer or esters of fatty acids.
- To evaluate the effect of use of an inorganic acid like HCl as the granulating medium on the *in vivo* absorption of this compound exhibiting a pH-dependent solubility behavior.

EXPERIMENTAL

Materials and Methods

- The physico-chemical properties of Clarithromycin sourced from different API suppliers was first evaluated for suitability in formulating an extended release tablet dosage form.
- Initially clarithromycin granules were prepared in a 1-5 L shear granulator by granulating drug and lactose monohydrate with binder solution comprised of PVP K29/32 in either water or 0.01N HCl .
- The dried and sieved granules were blended in a standard V-blender with different concentrations / ratios of suitable rate-controlling polymers as well as magnesium stearate.
- Alternatively, the drug was granulated with lactose and HPMC K4M using either water or 0.01N HCl, followed by blending with Magnesium stearate and colloidal silicon dioxide.
- The blends were compressed into replicate 500 mg tablet batches using either a Carver or Betapress and tested for dissolution using 900 mL of 0.1 M Na acetate buffer (pH 5.0) in a USP 2 apparatus.
- A 1000 mg clarithromycin tablet was prepared by compressing blends composed of API-lactose-PVP granules blended with only commonly employed tableting aids like talc, silicon dioxide, MCC and magnesium stearate at different levels.
- Two 1000 mg formulations, one granulated with water and the other with 0.01N HCl on a GMM-25 high shear granulator were tested in a 4-arm proof of concept study under fed and fasted conditions.
- PVP K29/32 was substituted by other commonly-employed tableting binders like PVP K90, HPC EXF, HPMC E15 and HPMC K100 in order to evaluate and select the most optimum binder for manufacture of robust 1000 mg tablets with acceptable hardness and friability.
- The tablets were provided with either a suitable Opadry over-coat or an enteric over-coat such as Eudragit® L100-55 or HPMCP-50.

RESULTS



DISCUSSION

- Extended release tablet formulations of clarithromycin were prepared using conventional ER matrix polymers as well as a novel approach based on drug release purely by tablet erosion.
- HPMC hydrates rapidly when in contact with water forming a protective gel around the tablet⁴, a property essential for providing extended release. HPMC of higher viscosity grade swells to a greater extent as it has a greater intrinsic water uptake property than that of a lower viscosity grade. High polymer content results in greater amount of gel being formed. As a result, a reduction in drug release rate is obtained⁵. The drug release from the HPMC K4M formulations is controlled by polymer swelling and erosion and follows zero order kinetics.
- Carboxypol 71G is a cross-linked polyacrylic acid homopolymer suitable for manufacturing of extended release tablets by direct compression⁶. Polyox water-soluble resins are nonionic poly (ethylene oxide) polymers forming hydrogels that regulate the drug release. Systems containing polyox resins often approach zero order release models⁷.
- Ethylcellulose is a water insoluble polymer that compacts well and also retards the drug release. In addition, matrices of this polymer display slow surface erosion which can be enhanced by the incorporation of suitable swelling agents, pore-formers or channeling agents⁸.
- Extended release formulations of practically insoluble compounds like clarithromycin can be formulated without the use of any rate-controlling polymers. In this case, the dosage form is composed of just commonly-used tableting aids, especially talc and magnesium stearate that are hydrophobic and serve as dissolution-retardants when used in excess of 1% w/w.
- Choice of the wet-granulation binder seems critical for this type of formulation. It was observed that for granules of this particular compound, HPMC E15 and HPMC K100 were superior to PVP K30, PVP K90 and HPC EXF. Tablets with HPMC as the binder were more robust (devoid of capping, sticking, etc), less friable and had little to no variation in their intra- and inter-batch tablet hardness and weight uniformity values.

CONCLUSIONS, REFERENCES AND ACKNOWLEDGMENTS

Conclusions

“Extended release tablet formulations of a practically insoluble compound clarithromycin can be successfully formulated with and without the use of conventional rate-controlling polymers”

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