Development and evaluation of sustained release pellet-filled capsules with simvastatin

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The strong positive relationship between plasma cholesterol and coronary heart disease incidence extends over a wide range of cholesterol concentrations. Effective lipid-lowering treatment has thus assumed an important role in the prevention of atherosclerosis and coronary artery disease. Simvastatin, an 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is the most effective in lowering plasma levels of total and lowering low-density cholesterol and are generally well tolerated.

It is of large interest creation of Simvastatin extended release capsules for treating hypercholesterolemia.

The goal of using extended release formulations is to maintain an effective therapeutic concentration of the active pharmaceutical ingredient (API) for an extended period of time. Especially medicines with a short half life are good candidates for this formulation. The rate of API release equals the rate of API elimination, thus ensuring that the API concentration is within the therapeutic window for about 24 hours.

Simvastatin has short biological half-life (3hr), high first-pass metabolism and poor oral bioavailability (5%) [1], hence an ideal candidate for extended delivery system.

The aim of the current study was to design an oral extended release capsules with pellets of simvastatin and to optimize the drug release profile.

The object of our researches was a substance Simvastatin that was supplied by «Harman Finochem Ltd» (India), pellets and capsules on its basis.

Simvastatin is a white to off-white powder that is practically insoluble in water and soluble in organic solvents such as ethanol.

Pellets are spherical granules coated with films of high molecular compounds. This medicinal form was selected because pellets may distributed in the intestine without creating a high concentration of the substance in one place [2].

The core pellets with simvastatin were prepared by extruder (plate with orifices) and spheronizer (dragee pan) using combination of spheronizing agent and disintegrant. The simvastatin (7 %), microcrystalline Cellulose Avicel pH 101 as spheronizing agent (39 %), lactose as filler (44 %), Kollidon CL (8 %) as disintigrant were mixed to form a uniform blend. The 2.5% polyvinyl pyrollidone (PVP) K-30 ethanol-aqueous solution as binder was slowly added in the mixture of powders to achieve a consistency of the damp mass suitable for extrusion-spheronization

technology. The prepared mass was passed through an extruder using 1 mm diameter screen. The extrudes were then placed to spheronizer. After that pellets were dried.

PVP K-30 gives binding properties to pellets for sufficient hardness to withstand mechanical tension in coating pan while superdisintegrant Kollidon CL acts by swelling mechanism.

Further, the drug loaded core pellets were coated using a dragee pan with different combination ratios of ethylcellulose (EC) and HPMC (hydroxypropylmethylcellulose) (0:100, 100:0, 75:25, 70:30, 65:35). EC is a water insoluble polymer, which have a relatively small degree of swelling due to its hydrophobicity. HPMC is a water soluble cellulose derivative that can be incorporated into EC films to alter permeability and is compatible with EC [2].

A coating suspension for sustained release pellets was prepared from HPMC, EC, magnesium stearate, ethanol and water. Magnesium stearate was an antifriction agent for diminution friction between the surfaces of pellets, the pellets-filling equipment and capsules.

The friability of uncoated pellets is an important parameter to withstand handling and coating. The friability was insignificant (0.49±0.22).

It was observed that the obtained coated pellets were uniform in size and shape (fig. 1). The uniform size of pellets indicates good content uniformity, good flowability (9 g/sec), bulk density (0.7 g/ml) and an easy process of capsule filling.

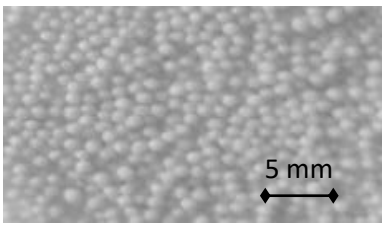

Fig. 1. The obtained pellets with simvastatin

Polymer coated pellets were filled in gelatin capsules (size 1) to study sustained release profiles.

The optimized composition of hydrophobic and hydrophilic polymers with EC and HPMC (65:35) was stabile by conducting accelerated test of stability for capsules.

Conclusions. The composition and technology of pellets and capsules with simvastatin have been developed as a result of the research. The influence of auxiliary matters on the technological indexes of the obtained pellets has been studied.

References

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