How to mimic the release kinetics of an OROS® formulation with EUDRAGIT® polymers

Felix Hofmann[1], Marcel Arndt[1], Daniel Juenemann[2], Theresia Kuntz[1]
[1]Evonik Nutrition & Care GmbH, Health Care, Darmstadt, Germany, felix.hofmann@evonik.com
[2]Midas Pharma GmbH, Ingelheim, Germany

Introduction

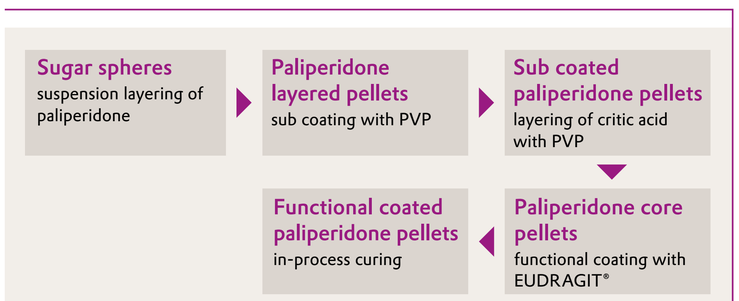
The number of marketed oral osmotically driven systems (OODS) has significantly increased in the last 15 years. The main benefit of OODS is the capacity to deliver drugs in a sustained manner, independent from the API's chemical properties, the patient's physiological factors or concomitant food intake [1]. On the other hand, compliance issues caused by the size of the tablets and high production costs are disadvantages of OODS. Also numerous patents are an obstacle for formulation development [2].
Moreover, the non-degrading cores of OODS can cause confusion in unstable patients. It was aimed to develop an alternative dosage form for a schizophrenia drug (paliperidone) with similar release properties as Invega® (paliperidone, Janssen-Cilag) by using conventional coatings.

Materials & Methods

Materials:
Pharm-a-spheres™ (sugar spheres) 1700 – 2000 µm (Hanns G. Werner GmbH & Co. KG, Germany), Kollidon® (polyvinyl-pyrrolidone, PVP) K 25 (BASF SE, Germany), Talc Pharma (Imerys Talc Italy S.p.A.), paliperidone (Megafine Pharma (P) Ltd., India), citric acid monohydrate (Merck KGaA, Germany), EUDRAGIT® FS 30 D (polymethyl acrylate-co-methyl metha-crylate-co-methacrylic acid) and EUDRAGIT® NE 30 D polyethyl acrylate-co-methyl methactylate) (Evonik Nutrition & Care GmbH, Germany), polysorbate 80 (Merck KGaA, Germany), Methocel™ (hydroxypropyl-methylcellulose, HPMC) E5 Premium (Dow Wolff Cellulosics GmbH, Germany), Invega® 9mg, batch BKZS900 (Janssen-Cilag, Beerse, Belgium)

Method:
Preparation of functional pellets:

Figure 1



Process flow chart for drug layering and functional coating

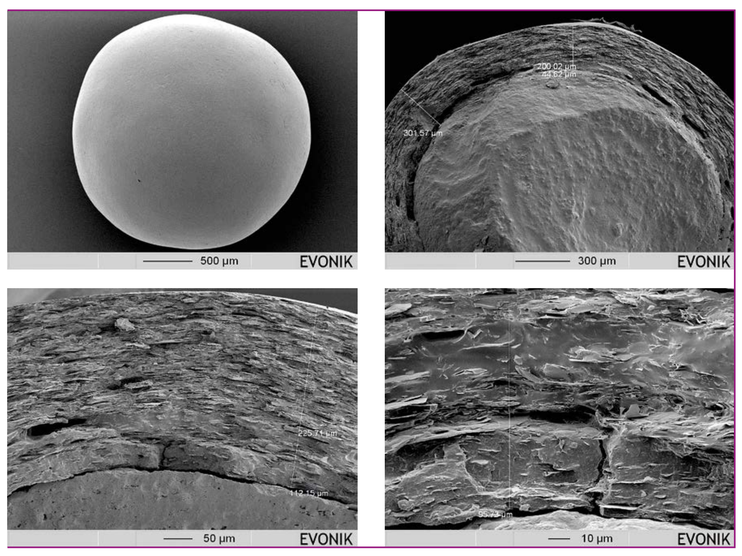
Paliperidone was suspension layered onto sugar spheres using PVP as binder. On the drug-layered pellets a PVP coating was applied as isolation layer followed by citric acid as pH buffer layer also using PVP as binder. Citric acid was used to create an acidic micro-environment since paliperidone shows a pH depen-dent solubility which is declining at increasing pH values. Finally, functional coatings of 8, 9 and 10 mg/cm² were applied on the pellets using a blend of the neutral sustained release polymer EUDRAGIT® NE 30 D and the anionic delayed release polymer EUDRAGIT® FS 30 D.
The functional spray suspension contained talc as anti-tacking agent, polysorbate 80 and HPMC as emulsifier and pseudo-emulsifier respectively. All spray suspensions were aqueous based and were applied using standard parameters as recommended in the EUDRAGIT® Application Guidelines. The coated pellets were in process cured at about 40°C product temperature and 45% relative exhaust air humidity. All coatings and the in process curing were conducted in a Huettlin Mycrolab (Hüttlin GmbH, Germany) fluid bed coater in bottom spray mode.

Scanning electron microscopy (SEM):
The pellets were placed on a mount with a conductive surface and were sputter coated with gold. For images of the cross section the pellets were frozen with liquid nitrogen and broken by means of a needle prior to the sputtering. The sputtered samples were placed into the scanning electron microscope (JEOL JSM-840A, Japan) and the images were prepared with a voltage of 5 kilovolt.

Dissolution Testing:
Dissolution tests were performed on USP II paddle apparatus (ERWEKA DT 700, Germany) at 37°C and 50 rpm in triplicate (n=3). Either 500 ml 0.0825 N HCl plus 2 g sodium chloride per liter adjusted to pH 1.2 or acetate buffer pH 5.5 USP were used as dissolution media respectively. Concentrations of paliperidone were analyzed via online-UV-measurement at 238 nm. Dissolution tests were conducted over 24 hours

Results and Discussion

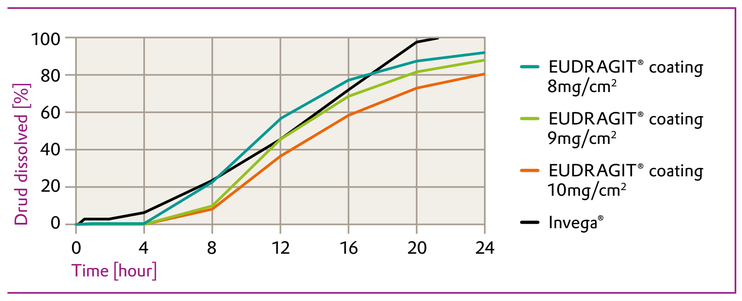
Figure 2



SEM images of the EUDRAGIT® coated final pellets showing the surface (top left) and cross-section (top right and both bottom images)

SEM images show homogeneous and smooth pellet surfaces free of cracks. The thickness of the functional coating was between 200 and 250 µm (Figure 2) at 10 mg/cm².

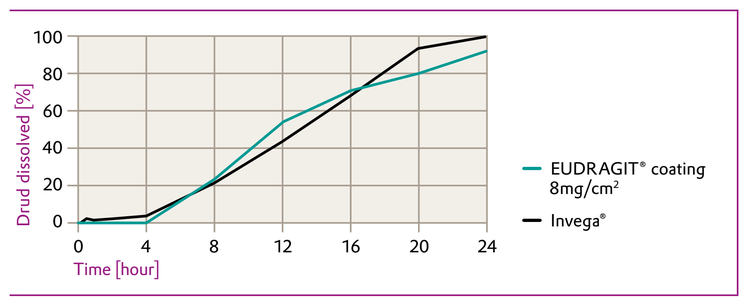
Figure 3



Dissolution profiles of paliperidone pellets with EUDRAGIT® coating compared to Invega® at pH 1.2

The dissolution kinetics of the EUDRAGIT® coated pellets could be adapted by the modification of the mass of applied coating layer. Comparing the similarity factors [3] the formulation with 8 mg/cm² coating (f2= 65.71) was superior to the pellets with 9 mg/cm² (f2= 57.08) and 10 mg/cm² (f2= 48.23) applied coating.

Figure 4



Dissolution of paliperidone pellets with EUDRAGIT® coating and Invega® at pH 5.5

While dissolution testing at pH 1.2 (Figure 3) was performed to mimic the gastric environment, pH 5.5 (Figure 4) represents the pH in the proximal duodenum [4]. Invega®, as an OROS® formulation, is known to show release kinetics which are independent from the physiological factors, such as varying pH during gastrointestinal passage. Paliperidone pellets coated with 8 mg/cm² EUDRAGIT® polymers provided a comparable time controlled pH independent dissolution behavior. The similarity factor of Invega® and paliperidone pellets 8 mg/cm² EUDRAGIT® polymers at pH 5.5 is 62.04.

Conclusion

The release kinetics of an OROS® drug delivery system can be mimicked by using standard cost effective production equipment like a fluid bed coater and well known controlled release EUDRAGIT® polymers. Furthermore, the complete process including drug layering, functional coating and curing, can be pictured in only one production equipment which supports cost-effective production processes. In contrast, Invega® utilizes a tri-layer core OROS® Push-Pull™ technology consisting of two drug layers and a push layer which is then surrounded by various coatings, followed by a laser drilling of two orifices [5]. The dissolution kinetics of Invega® were matched over the physiological pH range indicating similar in vivo release of paliperidone. The promising in vitro results will need to be verified in a bioequivalence study.

References

1. Malaterre V., Ogorka J., Loggia N., Gurny R. Oral osmotically driven systems: 30 years of development and clinical use. Euro. J. Pharm. Biopharm., 73, 311-323 (2009)
2. Santus G., Baker R.W. Osmotic drug delivery: a review of the patent literature. J. Control. Release, 35, 1-21 (1995)
3. EMA Guideline on the investigation of bioequivalence; CPMP/EWP/QWP/1401/98 Rev. 1/ Corr (2010)
4. Fuchs A., Dressman J. Composition and Physicochemical Properties of Fasted-State Human Duodenal and Jejunal Fluid: A Critical Evaluation of the Available Data. J. Pharm. Sci., 103, 3398–3411 (2014)
5. EMA Invega: EPAR – Scientific Discussion; 16/07/2007, http://www.ema.europa.eu