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REVIEW

NEW ORAL DRUG FORMULATIONS

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SUMMARY

During the past few years, the pharmaceutical industry has seen expirations on patents of some very important drugs, leading to major losses for their companies. This trend has not reached its end, with even more blockbuster drugs losing their patents in the upcoming years. In this context, the pharmaceutical industry has adapted by producing new delivery systems of the active component, which are able to increase product efficacy and patient compliance, rather than launching new chemical entities. These formulations include complex dosage forms such as transdermal, trans-mucosal and also new oral delivery formulations. In 2009, the number of reformulated products that were using these technologies was almost triple that of new chemical entities (75 versus 26). This article focuses though on novel formulations for oral delivery.
Key words: controlled release formulations, oral drug absorption system, patent

RÉSUMÉ

Nouvelles formulations de médicaments par voie orale

Dans les dernières années, l'industrie pharmaceutique a été confrontée à l'expiration des brevets des médicaments d'importance majeure, conduisant à des pertes substantielles pour les sociétés auxquelles ils appartiennent. Cette tendance ne se termine pas ici, encore plus de meilleurs médicaments perdront des brevets dans les années à venir. Dans ce contexte, l'industrie pharmaceutique s'a adaptée par la production de nouveaux systèmes pour la livraison du composant actif, qui sont en mesure d'augmenter l'efficacité du produit et le respect du patient, au lieu de lancer de nouvelles entités chimiques. Ces formulations comprennent des systèmes complexes tels que l'administration de formulations transdermiques, transmuqueuse et nouvelles formulations orales. En 2009, le nombre de produits en cours de reformulation qui ont utilisé ces technologies étaient près de trois fois plus grand par raport aux nouvelles entités chimiques (76 contre 26). Cet article se concentre sur les nouvelles formulations pour l'administration par voie orale.
Mots-clés: formulations de libération contrôlée, système d'absorption de médicament par voie orale, brevet

INTRODUCTION

Typically, basic EU patents last 20 years, but this period can be prolonged by changing the chemical form or the formulation of a product. Otherwise, a manufacturer can apply for a supplementary protection certificate, due to the lengthy time it took to develop the medicine. This can extend the marketing exclusivity of a product in the EU by five years.

Moreover, a 2007 EU regulation offered the possibility to extend the duration of a supplementary protection certificate by a further six months, in order to promote the development of medicines for children. This applies to all indications of a product, but the company must prove that the product can be used, or can potentially be used, in children.

Liquid Formulations

Delsym and Phentuss syrups have been formulated according to the Pennkinetic technology, a drug-polymer ionic complex where the polymer is an ion exchange resin. This has allowed controlled release of the active ingredient depending on the pH and the ionic strength of the delivery site. Within these systems, ion-exchange resins have permitted a sustained drug release, they have prevented dose dumping and have also made them abuse-

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resistant.

Micro-pump platform from Flamel Technologies uses micro-particles with the ability to target the site of drug release and can be adapted to the formulation of oral suspensions. It is especially useful for drugs which can only be absorbed in the small intestine.

LiquiTime platform, from the same company, involves a suspension of proprietary film-coated micro particles. The active ingredient is encapsulated in the core of the micro particles, leading to an effective masking of taste. The micro-particles have a homogenous size distribution of under 200 μm, leading to a smooth feel of the suspension in the palate. The formulation has long-term physical stability and reproducible performance, lasting over 2 years of storage. Similar to Micro pump platform, it can be employed for a combination of drugs with different release kinetics.

Liquid-filled Formulations

Liquid-filled hard and soft capsules can enhance the bioavailability of the active component by presenting it in a liquid or semisolid form, as do the self-emulsifying and self-micro-emulsifying systems.

Another advantage of these formulations is that they can improve the chemical stability of active ingredients that are sensitive to oxygen, light or moisture. They are typically dissolved in a non-aqueous liquid vehicle, compatible with the capsule shell. An example is Neoral soft gelatin capsules from Novartis, where a concentrated solution of cyclosporine in an oily vehicle undergoes spontaneous micro emulsification with gastro-intestinal fluids. The benefits of this formulation compared with the previous Sandimmun formulation are predictable and consistent absorption profile of cyclosporine, unaffected by the presence of food and bile in the GI tract.

Liquid-filled formulations are now a preferred choice also for highly potent drugs due to their capability of ensuring homogenous distribution of the active drug in the liquid vehicle, thus avoiding the low content uniformity problems encountered in powder fills.

Solid Dispersions

In order to solve the issue of low aqueous solubility of some drugs, lipophilic compounds with polymers at specific ratios to form solid dispersions or solid solutions are used.

Solumer technology is one example of a solid dispersion, forming a colloidal suspension on contact with the GI fluids. This leads to an increased dissolution rate of the drug.

Another system has been used for the reformulation of itraconazole to a product with enhanced bioavailability. SUBA-Itraconazole involves a solid dispersion of the active ingredient with a suitable polymer.

Oral dispersible Tablets

Rapidly dissolving tablets and thin films for systemic drug delivery are achieving popularity due to their easy administration, especially in patients with difficulty swallowing solid forms. These tablets can be formulated using direct compression and super-disintegrants such as croscarmellose sodium and crosspovidone.

Other methods involve patented technologies, such as the Zydis freeze-drying fast-dissolve technology by Catalent, which has already been used in the formulation of more than 20 commercial products, including loperamide hydrochloride.

Controlled Release Formulations

Sustained release of a drug involves polymers that release the active ingredient at a controlled rate due to the diffusion out of the polymer or by degradation of the polymer over time.

Nevertheless, pulsatile release is the preferred method of delivery most of the times. That is because it mimics the way that the body produces hormones such as insulin. And this is achieved by drug-carrying polymers that respond to specific stimuli like changes in temperature, pH or exposure to light.

OROS

The Osmotically controlled Release Oral delivery System, developed by Alza (Johnson & Johnson) is made up of a tablet core containing a water-soluble drug and osmotic agents (sodium chloride, sugars, hydrophilic polymers, etc.). This core is coated with a semi-permeable polymer such as cellulose acetate, which is permeable to water, but not to the drug. Within the GI tract, aqueous fluid enters the OROS tablet through this membrane and forces the drug out through a delivery orifice at a constant controlled release rate.

Nonetheless, poorly soluble drugs can be incompletely released, so Alza has developed the OROS push-pull technology, where tablets have multiple drug layers with a push layer (a water-swellable polymer) at the bottom. This layer pushes the solution from the upper drug layers out of the system through the delivery orifice.

L-OROS is another technology. It was developed for highly water insoluble drugs and it is a liquid-filled softgel coated with multiple layers, such as an osmotic push layer and a semipermeable layer. Within this technology, the internal osmotic layer pushes against the drug compartment and pushes the liquid drug from the delivery orifice present in the outer layers of a coated capsule. Glucotrol XL (glipizide extended release, Pfizer) is a classic example of an OROS tablet.

OCAS

The Oral Controlled Absorption System technology from Astellas Pharma incorporates a highly water-retaining polymer that drags and retains water during its transit through the GI tract and then uses the media in the colon (where there is little surrounding fluid) to ease release and absorption. This has been utilized to tamsulosin and branded as Omnic Tocas, showing higher night-time

plasma concentrations and no change of the pharmacokinetic profile by food.

TIMERx

This system forms a hydrophilic matrix in aqueous media and controls the drug release for 24 hours. By adjusting 2 constituent polysaccharides (xanthan gum and locust bean gum), different release profiles can be achieved. These polysaccharides slow down water penetration into the dosage form and control release of the drug. TIMERx is easy to manufacture, cost-effective, suitable to many different active compounds, with various drug loading and solubility. It also offers very satisfying patient compliance.

SODAS, CODAS and IPDAS

These technologies have been developed by Elan, according to the need of the drug.

Ritalin LA, used to treat attention deficit hyperactivity disorder in children, implies the SODAS (Spheroidal Oral Drug Absorption System) technology, where a combination of immediate and controlled release beads is incorporated within the system to obtain a pulsatile release profile of methylphenidate.

The CODAS (Chronotherapeutic Oral Drug Absorption System) allows drug release according to the circadian patterns of the disease. Verelan PM is a sustained release formulation of verapamil hydrochloride taken at bedtime, to give a higher drug release during the early morning hours, when heart attacks are more likely to occur.

Naprelan offers a controlled release of naproxen using IPDAS (Intestinal Protective Drug Absorption System) technology. This involves compressing high density micro particulate beads into tablet formulations. The tablets disintegrate into dispersion of beads throughout the GI tract to prevent dose dumping of the GI-irritant active ingredient. Mini-tablets are filled into capsules, having thus the advantages of both tablets and micro-particular dosage forms.

Systems Targeting the Stomach and Colon

Encap has used the ENCODE technology to target the delivery of capsules to the colon. The ENCODE Phloral system is triggered by both the microbes in the colon and the pH to deliver the drug accurately and consistently.

Alizyme`s Colal system delivers prednisolone topically to the colon to treat ulcerative colitis. This is similar to the efficacy of the standard oral prednisolone, but without the side-effects usually associated with steroids, by using a coating that is only broken down by the microbes in the colon.

The Multi Matrix MMX technology by Cosmo is a pH-resistant acrylic co-polymer that delays the release until it reaches the pH of the targeted location in the intestine, allowing controlled release over the length of the colon. This has been used for the treatment of mild to moderate ulcerative colitis with budesonide.

Combination Technologies

DuoCap by Encap Drug Delivery is a capsule-in-capsule technology that allows the incorporation of different drugs in one formulation. The inner and outer capsules usually contain different types of formulations. The inner part may comprise liquid, pellets or semisolids, while the outer part may have liquid or semisolids. Also, the site of the drug release along the GI tract and the release kinetics of the inner and outer capsules can be different by incorporating appropriate coatings.

Combodart by GlaxoSmithKline, indicated for the treatment of benign prostatic hyperplasia, has got an outer hard capsule containing tamsulosin hydrochloride as modified release pellets and an inner soft capsule containing dutasteride.

Injectables Switched to Oral Formulations

Generex Oral-lyn by Generex Biotechnology is a new oral insulin spray formulation and delivery system which provides an alternative to injectable and inhaled insulin. This system allows a liquid oral spray insulin formulation to be delivered into the mouth via an aerosolized spray that uses a proprietary delivery system (RapidMist Diabetes Management System). The technology uses the formation of micro-fine micelles made from a combination of absorption enhancers that encapsulate and protect the insulin molecules for safe and effective delivery via trans-mucosal absorption in the oropharyngeal cavity. The active ingredient is recombinant human insulin, still the formulation behaves more similar to the synthetic fast-acting insulin analogues. It was shown to be absorbed in direct relation to the amount given and had a faster onset and shorter duration of action, compared to regular insulin given subcutaneously.

Emisphere Technologies has announced the success of its soft-gel capsule formulation of unfractioned heparin in a clinical trial. The Eligen Technology, Emisphere`s broad-based oral drug delivery technology platform, is based on the use of proprietary synthetic chemical compounds known as Emisphere delivery agents or "carriers". These molecules facilitate or enable the transport of the therapeutic macromolecules across biological membranes such as those of the gastrointestinal tract and exert their wanted pharmacological effect.

Abuse-resistant Mechanisms

Abuse-resistant formulations are delivery systems for scheduled drugs (opioid analgesics, narcotics, etc.) that deter consumers either from extracting the active ingredient or from experiencing euphoria by inappropriate use.

Gel-Cap technology, by Pain Therapeutics and King Pharmaceuticals, makes use of gelatin capsules filled with a material called sucrose acetate isobutyrate (SAIB). This gelatin capsule dissolves when administered by oral route and the drug is released in a controlled manner from the SAIB matrix. The active compound can`t be extracted out of the capsule because of the low aqueous solubility of the SAIB and it can`t be snorted as cause of the SAIB`s high viscosity and it's adhesive capacity. Dosage forms using this technology are currently under clinical trials.

Another system is Trigger Lock from Flamel Technologies

which contains micro-pump particles that are crush-resistant, deterring the user from extracting the active ingredient.

Abusolve by Encap Drug Delivery uses a technology based on liquid-filled hard-shell capsules, where the filling material consists of waxy and thickening agents. It has a high melting point and unpleasant-tasting excipients or taste modifiers that prevent extraction, snorting or injecting the active drug.

Conclusions

The introduction of new chemical entities is very low at the moment. There is also an increased demand for a higher number of complex clinical trials, which is prolonging time to market. This is why the pharmaceutical companies are trying to come up with controlled release formulations of existing immediate release products, leading to a re-patentability of their products.

References

1. Nazar Hamde, Dodou Kalliopi, Research and Development in Oral Controlled Release Drug Formulations; The Pharmaceutical Journal, vol 288/7704, May 2012; 567-568
2. Nazar Hamde, Dodou Kalliopi, Oral Formulations Adapted for the Old and the Young and to Prevent Misuse; The Pharmaceutical Journal, vol 288/7708/9, Jun 2012; 683-684
3. Pozzilli Paolo, Raskin Philip, Parkin Christopher, Review of Clinical Trials: Update on Oral Insulin Spray Formulation, Blackwell Publishing Ltd., 2009
4. Taheri Leila, Winners and Losers as Many Medicines Come off Patent in the Next Two Years; The Pharmaceutical Journal, vol 288/7703, Apr 2012; 512-513
5. http://ir.emisphere.com/releasedetail.cfm?ReleaseID=356301