CHALLENGES AND OPPORTUNITIES ON FORMULATION AND DEVELOPMENT OF FIXED DOSE COMBINATIONS: UNIGEL®, A TECHNOLOGICAL PLATFORM

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ABSTRACT

This article is aimed to offer a general review of the fixed dose combinations (FDC), the manufacturing technologies and their applications, benefits and setbacks as well as a case study to illustrate the product concept based on the technological platform of Unigel® for FDCs in soft gelatin capsules

INTRODUCTION

The fixed dose combination (FDCs) systems were mainly aimed to increase the patient compliance to the pharmacological treatments composed of two o more active drugs in a single dosage form, in order to decrease the number of doses and the prescription problems. The Food and Drug Administration (USA) defines a combination product as 'a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product.

Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance (1).

From the clinical standpoint, a good fixed dose combination were aimed at lower doses used, higher efficacy, lower rates of adverse events, and reduced pill/injection burden on patients. At the end, the combination of some of these benefits will be translated in an overall increase on therapy adherence, particular in the treatment of chronic diseases (2). It is unclear whether this satisfaction will translate into long-term increases in adherence and ultimately better outcomes which can lower the overall costs of care, but in any case, detailed clinical studies and claims data analyses are required to prove the value of fixed combinations (3)

A recent WHO report indicated that the simplicity of the dosage regimen and side-effects were the therapy-related factors that had the greatest influence on adherence to long-term therapies. The complexity of self-administration increases rapidly with the use of multiple therapies for the same condition or for several conditions in the same patient, and there is a consequent reduction in adherence (2).

Monotherapy vs. FD&C: FDC applications

Combinations of medicinal products are administered in a number of scenarios to improve clinical outcomes for patients. As a general brief, the indications for the FDC development and their potential advantages cover:

- **Sinergy:** The effect of the combination is superior to the individual effects. It offers a greater overall effect and/or is more rapidly effective.
- **Adverse effects:** The combination improves safety due to one active substance counteracting the adverse drug reactions of another or by combining doses that are sub-therapeutic when used in monotherapy.
- **Different action mechanisms for a treatment indication:** The treatment of complex diseases with many pathophysiologic contributing factors that require multiple modes of treatment, targeting different pathways, such as diabetes or hypertension.

It is the case of type 2 diabetes, where lower doses of two agents can be used instead of a high dose of one agent, this can reduce the side effects that often occur with a high dose of the one agent [12, 13].

- **Treatment of multiple diseases or medical conditions**. For example, the FDC amlodipine besylate 2.5 mg/atorvastatin calcium 10 mg is prescribed to treat hypercholesterolemia and high blood pressure and thus lower the risk of heart attacks and other deleterious cardiovascular events (3).

- **Simplify administration,** where a combination of active substances is already recognized with an existing therapeutic claim, and reduces the mistakes associated to the drugs prescription or administration. It also reduces the costs associated to packaging that accounts for more than 50% in OTC products and it also can half the prescription costs to the healthcare system, considering that it reduces the prescription of two or more drugs to one (4).

- **New therapeutic claim,** alternatively, a fixed combination medicinal product may be developed de novo to address a new therapeutic claim.
- **Lyfe cycle extension.** Patent expirations for the individual components in the market might result in FDC development to extend the marketing of these products. They also can indeed be patented as a novel chemical entity as a way to extend proprietary rights and marketability of the pharmaceuticals.

Note that in general the mentioned advantages are common to the available technologies for FDC, however not for all of them it is possible to develop the concept based on the following product criteria:

- Incompatible APIs
- Different release profiles for different APIs or dual release for an API (immediate, extended and/or modified release)

Technologies for FDC manufacturing and their applications

Diverse technologies have been developed for the manufacturing of FDC products, being the more representative the technology of multilayer tablets and the hard capsule for FDC. There are also some other technologies such as compression coating, active coating, bilayer floating tablet y buccal/mucoadhesive delivery systems, but we are aimed to mention some of the present challenges for the manufacturing of FDC using the multilayer and hard capsule technologies (5):

1. *Multilayer tablet technology*

   It is based on the compressing of granules of two or more APIs as different layers in one tablet. Beside the API layers, it could contain layers of non functional placebo to avoid the interaction between the layers of incompatible APIs

   The main considerations applying this technology for FDC development are the inclusion of placebo layers, APIs and excipients load, dosing accuracy and the fact that is not suitable for liquid or semisolid APIs.

2. *Hard capsule for FDC technology*

   This technology comprises the inclusion of different types of solid oral dosage forms inside of a hard capsule in order to combine different APIs or different release profiles of one or different APIs. In contrast to the multilayer technology, considering that the dosage forms are individual entities, physical barriers are not required to deal with the issue of incompatible API. Some variations of the original system allow the dosing of liquid, semisolid, powdered, granuled or pelleted APIs into the hard capsule (6).

   Based on its concept, some of the considerations to apply this technology are excipient load, coatings, space constraints, flow of solid dosage forms (powders, granules, microcapsules, pellets), APIs load and the requirement for banded hard capsule technology.

3. *Soft capsule for FDC technology*

The Unigel® technology is a patented invention that covers a machine and a manufacturing process to obtain soft gelatin capsules containing internally other solid

dosage forms such as granules, soft or hard capsules, tablets, extended or inmmediate release forms and zero order release solid dosage forms. The soft gelatin capsule is a fixed dose combination particular, but not limited to physical or chemically incompatible APIs in one convenient and trust oral dosage form that is stable during its shelf life. Compared to conventional SGC dosage forms, it allows to combine liquid and solid APIs and to stabilize FDC, formulating incompatible components separately in the liquid phase or the tablet. In contrast to the products obtained by the FDC technology for hard capsule, the Unigel® products offer the benefits of the soft gelatin capsule, the convenience for its administration in terms of size and swallability, the avoidance of the counterfeit risk and the innovation in the product concept. . In terms of stability, compared to the hard capsule technology, the soft capsule process avoids any headspace that affects the stability of APIs prone to oxidation and it could be also adapted for encapsulation using inert gases. Compared to the hard capsule FDCs, in the one tablet- soft capsule FDCs, the APIs load is higher, the space constraint is lower and the liquid dosage could be as high as 1000 mg/caps.

Case study. Omega 3

Based on the sinergical effects of APIs in FDC, interest has grown to cover the real benefits of the omega 3 supplementation in the pharmacological therapy of some chronic diseases and the possible options to formulate its supplements or pharmaceutical associations. The anti-inflammatory effects of omega 3 offer a wide spectrum of benefits in many body systems such as brain, heart, joints and eyes, and particular, as a secondary prevention of the cardiovascular events due to its inhibition of the platelet aggregation. Several studies have dealt with the association omega 3, acetyl salycilic acid and clopidrogel, resulting in a decrease on cardiovascular events and that support their use as FDC in safety and efficacy (7)

On the other side, as dietary supplement, a proprietary research from the global organization for EPA and DHA Omega 3s (GOED), showed in it survey that 57% of the American adults consume omega 3 from one or more sources (supplements, food or fish). It is expected that increasing the awareness of the omega 3 benefits will encourage more product development to satisfy the consumers expectations for new and creative delivery systems of omega 3 supplements.

EPA and DHA are the most studied compounds in human randomized controlled trials, inclusive of pharmaceuticals. Besides its benefits in human health, some studies have been shown in USA for every race and every age group that more than 90% of the population has omega-3 levels lower than are required for cardioprotection (7).

CONCLUSIONS

Until these days, the FDCs product development is growing in accordance to their applications in the pharmacological treatment of the most prevalent chronic diseases such as cardiovascular disease, diabetes and hyperlipidemias as well as for OTC products such as analgesics and antiacids. There is also a great expectation in the product development for dietary supplements. Furthermore, the benefits on therapy adherence are well recognized and some others due to sinergical effects of the APIs have been proved. The selection of the appropriate technology for FDCs manufacturing should consider the product criteria and the technological limitations in each case. In this regard, soft capsules FDCs technology was developed in the latest years and offers a technological platform for product development based on the benefits of the SGC and its particular features compared to the previous technologies.

REFERENCES

1. Gautam CH, Saha, L. Br J Clin Pharmacol (2008), 65(5), 795–796
2. Mathon, J. Fixed Dose Combinations in Type 2 Diabetes – Perspectives from the ADA Meeting and Future Development (2017)
3. Duconge, J, Ruaño, G. Pharmacogenomics (2015) 16(15), 1685–1688
4. Tugrul T. Kararli, TT., Sedo, K. Fixed-dose combination products- A review (Part 1 Introduction). Drug development and delivery, april 2014. http://www.drug-dev.com/Main/Back-Issues/661.aspx?format=2
5. Desai D., Wang J., Wen H., Li X., Timmins P. Formulation design, challenges, and development considerations for fixed dose combination (FDC) of oral solid dosage forms. Pharm Dev and Tech (2012)
6. Koo O. Manufacturing Process Considerations for Fixed-Dose Combination Drug Products. Am Pharm Rev (2010)
7. GOED. Opportunities in the global EPA+DHA omega 3 industry (2016)