

CHALLENGES AND OPPORTUNITIES ON
FORMULATION AND DEVELOPMENT OF
FIXED DOSE COMBINATIONS: UNIGEL®, A
NEW 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 new technological platform of Unigel® for FDCs in soft gelatin capsules



INTRODUCTION

The fixed dose combination (FDCs) systems were mainly aimed to increase patient's compliance to the pharmacological treatments composed of two or more active drugs in a single dosage form, in order to decrease the number of doses and 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 a 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:

- Synergy: 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 a lower dose 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 are already recognized with an existing therapeutic claim, and reduces the mistakes associated to the drugs prescription or administration. 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.

- Life 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 representatives the technology of multilayer tablets and the hard capsules for FDC. There are also some other technologies such as compression coating, active coating, bilayer floating tablet and 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 it is not suitable for liquid or semisolid APIs.

2. Hard capsules 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 immediate 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.

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, the avoidance of the counterfeit risk and the innovation in the product concept. Compared to the hard capsule FDCs, in the one tablet- soft capsule FDCs, the API 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 synergical 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 salicylic 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 its survey that 57% of the American

adults consume Omega-3 from one or more sources (supplements, food or fish). The expectation is 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 cardio protection (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 antacids. 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 synergistic 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.

To know more information on Unigel® technology and formulations visit <http://softigel.com/pharmaceutical-manufacturing/Softgels/unigel-softgels.aspx> or contact us at softigel@procaps.com.co

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.drugdev.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)

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