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Possible Protocol for Deformulation Studies for Pharmaceutical Products

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Abstract

The word formulation describes the formation of the product using various methods. While deformulation being the reverse of the formulation describes the deformulating the various components using different methods. One of the main and basic priority in the individual's life is money. So, to get and save money is one of the motives of every person even in the case of medicine. Here, lies a basic problem. Due to certain circumstances medicine acts as a toolkit in one's life. So, to save money and get the medicine at an affordable price is one of the basic demands of the society and many industries work on it forming the basis of generic drug production from the reference listed product. To prepare the generic product requires lot of efforts so with the advancement of technology a study named as deformulation also referred to as reverse engineering is a basic requirement for the preparation of generic product from reference listed drug. As India is known as the pharmacy of the world, in manufacturing of the generic products. So, there is an increasing demand of reverse engineering or deformulation studies. To carry out these studies there is no possible protocol available till date. So, this review will focus on the required protocol to carry out deformulation studies.

Keywords

Deformulation, Reverse Engineering, Protocol, Generic Product

1. Introduction

Engineering being defined as two ways forward engineering and reverse engineering. Dealing with the reverse engineering it involves the replication of the prevailing component or the product itself. It involves the comprehensive analyses of the components by identifying a system's components, creating the polymorphic and physical illustrations of the system. It is basically applied by the manufacturer to outgrow a patent on rival's manufacturing process. It is quiet common technique to investigate the components of the unknown product or the competitor's product. As India is known as world of pharmacy (in the manufacturing of generic product) so to develop a generic product, the pharmaceutical deformulation process starts even before the expiry of the patent product. It involves both qualitative as well as quantitative analysis of the components. As it is time consuming process so the innovator has to start with the process long before the expiry of the patent of the product so as to file ANDA as soon as possible. Here lies the first come first get situation this means the one who will file the ANDA application firstly will get the marketed product at first [1]. The objective of the entire process is to launch a bioequivalent generic product of a successful original product at earliest. According to *Bansal and Koradia 2005; Zhou* et al. 2018, a generic product must have similar properties, quantity as that of the reference listed product. As there are no guidelines available for the deformulation studies so a possible protocol is needed so as to follow the step wise procedure for these studies. So, this review basically deals with the protocol development to carry out these further studies [2].

1.1 Objectives of Deformulation Studies

To avoid any competition in the near future the competitor or the patent holder keeps the master formula as a secret. So, at any point of time regulatory agencies maintain the innovative formula as a proprietary and usually does not disclose to generic product companies. Therefore, it a competition of the great level and the production of generic product starts longer before the date of expiry. So, the basic objectives of the reversal process of formulation is to replicate a system or its subsystem having no prior exact knowledge of its components, manufacturing process, documentation for the approval of ANDA, safety and stability issue determination of the pharmaceutical formulation.

1.2 Applications of Reverse Engineering

Figure 1. Various Applications of Reverse Engineering Process.

1.3 Common Analytical Methods for Reverse Engineering Process

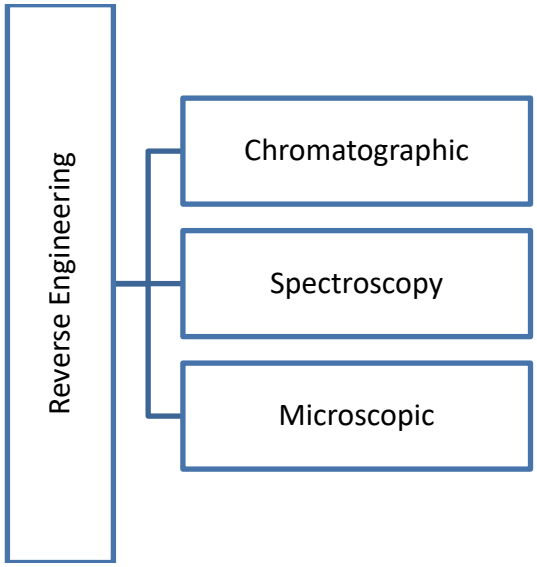

Figure 2. Analytical Methods for reverse engineering.

At each step of deformulation studies different analytical techniques are required. For accurate and precise identification of both qualitative and quantitative data most commonly HPLC and GC-MS are applied. For less volatile components LC-MS is used while for more volatile components GC-MS is used. These techniques are helpful to identify quantitative amount of the components in the entire formulation. While HPLC is known to be one of the

robust methods for separation of the components [3-6].

2. Possible Protocol for Deformulation Studies

As production of the generic product is the key objective of the reverse engineering process. As the basic necessity is that the generic product should both qualitatively and quantitatively match the RLD product so the entire process can be divided into four major parts [4]. The study starts with the procurement of the innovator's product and their physicochemical characterization. The physicochemical characterization includes the determination of the properties including melting point, polymorphism, oxidation, reduction, hydrolysis and other such properties. The second part includes separation and decoding various components of the formulation using different analytical methods including chromatography, spectroscopic and microscopic methods. The third part includes the solid-state characterization of API and excipients whereas the fourth part consists of identification of the manufacturing process. After this the formulation is further reformulated and the innovators and generic drug is compared by comparing the dissolution profiles of the two products and further f1 and f2 factors are determined to prove bioequivalence and for further filling up the ANDA. To be considered a generic product identical to innovator product, the similarity factor in in vitro dissolution profiles of both the products should be 100, while similarity factor (f2) of more than 50 indicates that the generic dosage form has a comparable dissolution profile to innovator product and may achieve bioequivalence status. During the deformulation of RLD product two important aspects must be determined including dissolution profiles and stability of the product [7, 10].

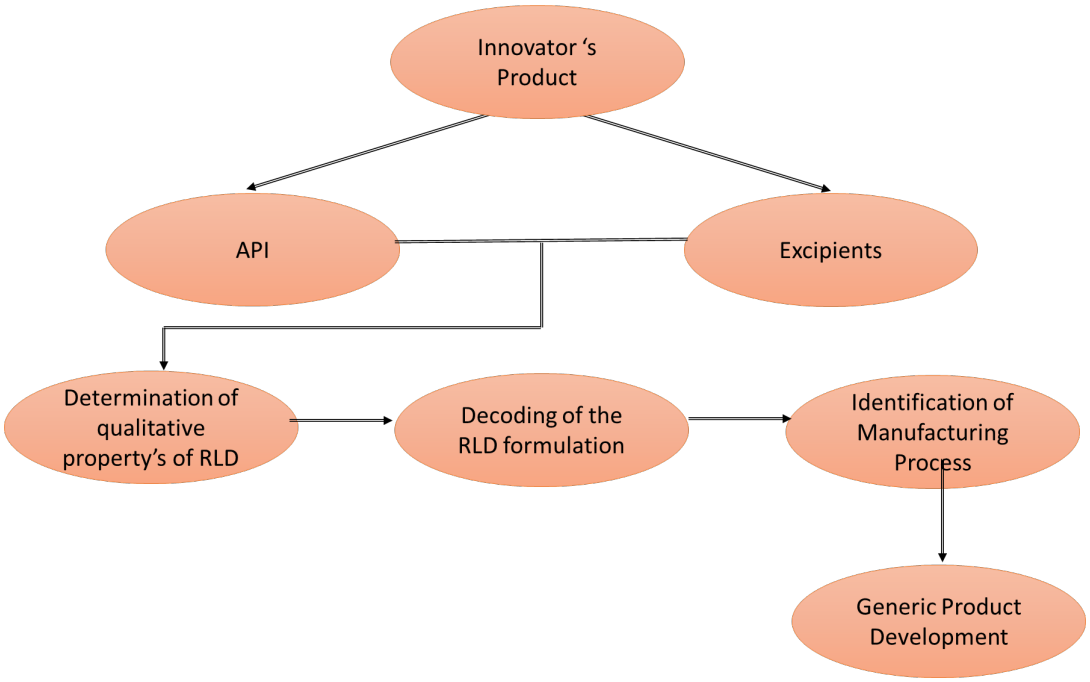

Figure 3. Possible Protocol for Deformulation Studies.

Step wise procedure for deformulation studies [17]

Literature analyses

The RLD's qualitative makeup is available in the public domain. The open section of the innovator firms' "summary basis of approval," which is submitted, is a useful resource for generic companies. On the USFDA website, click "Drugs@FDA" to view this. There is also helpful information in several popular sources like Physicians' Desk Reference and product information booklets.

Physicochemical Characterization

The physicochemical characterization includes the determination of the properties including melting point, polymorphism, oxidation, reduction, hydrolysis and other such properties.

Decoding the quantitative formula

Identification of crucial excipients and quantification of the identified excipients in the dosage form are the next two phases in decoding the quantitative formula of the RLD.

Finding the excipients that have a significant impact on the stability or functionality of the medicinal product

should be the first step in developing an RLD quantitative formula. Such ingredients may be referred to as crucial ingredients. Examples include wetting agents for hydrophobic drugs, pH modifiers/buffers for pH-sensitive drugs, solubilizers and dissolution modifiers such as surfactants for BCS class II and IV drugs, pH modifiers/buffers for pH-sensitive drugs, and stabilizers/antioxidants in formulations containing drugs that are susceptible to oxidative degradation. This helps in prioritizing resources for de-formulation studies

The next step is to quantify the essential excipient(s) in the solid dosage form, which can be difficult given the possibility of excipient interference. Therefore, the process of quantifying excipients requires two steps: the separation or extraction of the chosen excipient(s) and the measurement of the extracted excipient. Differential solubility, filtration (using filters with a specific pore size or molecular weight cut-off), high performance liquid chromatography (HPLC), high performance thin layer chromatography (HPTLC), and size exclusion chromatography are techniques that can be used to separate the excipient from the tablet matrix.

After separation, a gravimetric or detection technique must be used for quantification. The most effective method for quantifying important excipients with substantial weight ratios in the dose unit is gravimetry. Utilizing sophisticated separation and quantification techniques like HPLC and HPTLC, it is preferable to quantify components that are present in minute quantities, such as stabilisers, surfactants, and pH modifying agents. Size exclusion chromatography can be used to efficiently quantify high molecular weight excipients such polymers.

Solid State Characterization of the API

From a pharmaceutical perspective, the solid state properties can be divided into molecular, particle, and bulk level categories. Properties like crystalline forms, hydrates, solvates, co-crystals, and amorphous forms are all included in the molecular level. These forms differ in terms of solubility, manufactureability, bioavailability, and stability due to variations in intermolecular configurations and free energy. When developing generic goods, these variables are crucial for identifying the API solid form of the RLD.

To prevent solid form alteration during processing and storage, the most stable polymorphic form is typically used to generate the innovative product. To assure a similar stability and dissolution profile, generic firms adopt the same polymorphic form as the RLD as a safeguard. Sometimes an approach like this is prohibited by a polymorphic form patent that is still in effect after the fundamental molecule patent has expired. In this case, one may file under paragraph IV certification (505 [j] [2][A][vii]) and develop the generic product using an alternative solid form.

Solid forms can be characterised using a variety of methods, including powder X-ray diffraction, FTIR, NIR, and Raman spectroscopy; differential scanning calorimetry; themogravimetric analysis; and hot stage microscopy.

Identification of the Manufacturing Process

The physicochemical profile of the API can be utilised to anticipate the RLD manufacturing process; for example, water-sensitive APIs won't be able to undergo wet granulation. In a direct compression approach, it could be challenging to achieve mix uniformity of a very low-dose API. Visual analysis of the tablet fracture gives some insight into the granulation process. Fractures created by wet or dry granulations are harsher than those created by direct compression.

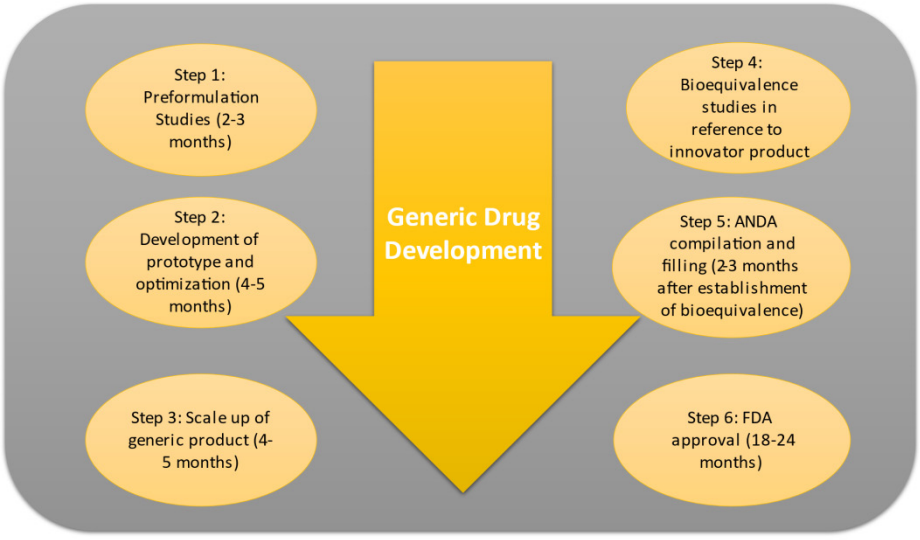

Figure 4. Steps involved in the generic product development.

2.1 Possible Protocol for Deformulation of Tablets

In case of tablets firstly for the qualitative analyses physico chemical characteristics are determined. The quantification of the tablet matrix is the second step which involves differential solubility, gradual filtration and various chromatographic techniques for the estimation. The techniques like XRD, DSC can be employed for determination of API of RLD [11, 14, 16].

2.2 Possible Protocol for Deformulation of Capsules

At first there is a need to decode the marketed formulation using different analytical methods including differential solubility technique. Based on the decoded formula a generic product can be prepared [12, 13, 16].

2.3 Possible Protocol for Deformulation of Herbal Products

Most of the herbal products being polyherbal formulation contains phytoconstituents. At first hydrophilic and hydrophobic compounds can be decoded separately followed by determination of entrapment of the ingredients in submicron vesicle using chromatographic techniques. The step is followed by determination of particle size using microscopy. Polar solvents can be extracted by polar solvents whereas non-polar using non-polar solvents [8, 9].

2.4 Role of Reverse Engineering for Stability Testing of Newer Drugs

The information of the RLD is available in the official monograph. But if the purity of any new drug is to be determined and no information is available in the monograph one can develop their own methodology for development of qualitative stable product. Further the estimation of the stability can be carried out using stress and accelerated stability testing [15].

2.5 Characterization of Innovator Products to Support Regulatory Submissions

The Hatch-Waxman Act (Drug price competition and patent term restoration act, 1984), which eliminated the need for duplicate clinical trials by allowing generic companies to use reference data that innovator companies provided to the agency in their new drug application (NDA), facilitated the development of generic drug products in the United States (US). According to the U.S. Food and Drug Administration (USFDA), a generic drug product can replace a reference listed drug (RLD) based on therapeutic equivalence, which includes pharmaceutical and bioequivalence. It is also possible to use data from RLD de-formulation studies to support regulatory submissions like biowaivers (waivers of bioequivalence studies). When it comes to the similarity of drug products, the USFDA has proposed the Q1 and Q2 concepts. While Q2 shows a quantitative resemblance between the products, Q1 shows a qualitative similarity. The phrase "quantitatively essentially the same (Q2)" denotes that the level or concentration of the inactive ingredient(s) in the test product would not deviate from the RLD by more than 5%. In situations where a pharmacokinetic end point is not a reliable indicator of the bioequivalence, the USFDA has also permitted biowaivers [17].

3. Conclusion

Deformulation, also known as reverse engineering is an important tool for genric product development. This method can be further used for the validation and estimation of the compound using different analytical methods. Although this is one of the most applicable methodologies for generic product development, we found very little information published in the form of publications due to market competition and being first in approval and launching of a generic product once the patent expires related to innovator product. Since many newer technologies are emerging day by day, a skilled and systematic approach may be useful in the development of the generic product of complex systems like nanomedicine and nanopharmaceuticals in the near future.

Conflict of interest

We declare no conflicts of interest.

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