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Review Article

PREFORMULATION STUDIES FOR AYURVEDA DRUGS: A REVIEW

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ABSTRACT

The vast treasures of drugs included in Ayurveda are obtained from various sources including plants, metals, minerals and animal products. These may further be classified into single drug and multi drug formulation compositions. Advancements in pharmaceutical industry have led to emergence of new class of drugs known as phytopharmaceuticals, where a single molecule or the principle metabolite of a botanical is extracted and used as a single drug. However, this concept does not collate with the treatment principles mentioned in Ayurveda texts. The industry should develop new compositions keeping the basic principles of Bhaishajya Kalpana (Ayurvedic Pharmaceutics) and chikitsa (therapeutics) in foresight. It is where the preformulation plays a major role in developing rational, safe and efficacious Ayurveda drugs. The conventional techniques of preformulation R&D may not be effective for Ayurveda drugs and there is a need to modify its structure in order to formulate new drugs. A lot is known about the properties of single drugs as well as multi ingredient formulations from the ancient texts and this knowledge can be effectively utilized by the industry during the preformulation R&D. Studies on solubility, dispersibility, hygroscopic nature, bulk forming, interaction of ingredients and binding properties must be conducted. The combinations of Ayurveda drugs should be studied and modified pharmaceutically to generate an effective single pill. The paper deliberates on this issue so that a technology friendly and scientifically advanced research and development of new Ayurveda products may be undertaken and exploited commercially for the benefit of ailing mankind.

Keywords: Ayurveda, Preformulation, safe and efficacious medicine.

INTRODUCTION

Ayurveda, the ancient science of life has a wide treasure of therapeutics in its armoury. This system, also known as traditional or complimentary medicine in many parts of the world derives its resources from knowledge embedded in ancient wisdom of texts documented centuries ago. However with the advancement of modern technology, scientific advancements, consumer awareness and the advent of evidence based medicine, attention has been given towards the quality control, marketing and development of new Ayurveda drugs.[1] A large part of the formulations used in Ayurveda have herbs/botanicals as ingredients, although some may be made with minerals, metals, and ingredients of animal origin. Ayurvedic formulations are currently industrially manufactured into products adopting large-scale technologies that pharmaceutical or food industry uses. Ayurveda mentions a number of pharmaceutical processes for manufacturing various dosage forms.[2] The traditional Ayurveda pharmaceutical industry employs water, milk or fatty acids (ghee, oil) as a medium or solvent for extraction of active metabolites from botanicals or concentrated decoctions. These may further be utilised as semi solid mass (avaleha) or dried powder and may be formulated as pills.[3] Worldwide a billion dollar herbal pharmaceutical industry is growing by leaps and bounds due to a renewed interest in herbal medicines globally, however, issues such as authentic raw material, standard manufacturing processes, inadequate quality control, and contamination of certain Ayurvedic drugs; are a serious problem which must be addressed. Ayurveda drugs have a wide window of opportunity to establish itself as a validated form of safe and efficacious medicine. The main burden of this lies on the capacity of therapeutics of Ayurveda to generate result oriented medicines. Industry exploits the knowledge of Ayurveda texts and combines it with modern technology, like separation of single chemicals or active ingredients, but this does not incorporate the essence of Ayurveda. This paper targets this issue so that a technology friendly and scientifically advanced research and development of new Ayurveda products may be undertaken keeping the essence of Ayurveda intact so that it may be exploited commercially for the benefit of ailing mankind.

Traditional methods of drug formulation

Ayurveda texts are full of both single and multi-ingredient formulations which are used for a wide range of therapeutic actions. The composition of these formulations is based on actual experiences of our ancient sages. Exploring this concept in depth, one can find that the properties of ingredients of these formulations are synergistic to each other. The properties of these ingredients can be categorised in to six sections namely, rasa, guna, veerya, vipaka, prabhava and karma.[4] These can be described as following:-

1. Rasa (sensation of taste perceived by the tongue after coming in contact with a drug): A total of six different tastes have been described which include Madhura (Sweet), Amla (Sour), Lavana (Salty), Katu (Pungent), Tikta (Bitter), Kashaya (Astringent) Every rasa is made of two out of the five mahabhoots (basic elements). Each of these rasa has specific effect on tridosha.
2. Guna (properties): It refers to specific properties that the drug possesses.

3. Virya (Potency): It is the energy that a herb releases during digestion. It can either be sheeta (cooling) or ushna (heating). The sweet, astringent and bitter herbs are said to have sheet virya, which refreshes body as well as reduces irritation and inflammation; while the ushna virya is obtained from sour, salty and pungent herbs that improves circulation, promotes sweating and helps digestion.
4. Vipaka (Post-digestive effect): It refers to the post digestive effect that a drug has on the body. It is of three: Madhura (sweet), Amla (sour) and Katu (pungent), each having different effects on the dosha.
5. Prabhava (Unique power of an herb): Some drugs have variable action on body which cannot be explained on the basis of rasa, guna, virya or vipaka. These specific manifestation or unique effect is termed as prabhava.
6. Karma (therapeutic action): It is the therapeutic manifestation of the drug on the body. It can be classified as Anuloman (Carminative), Deepana (Stimulant), Pachana (Digestive), Rasayana (immunomodulatory), Shodhana (Purification), Vajikarana (aphrodisiac) Virechana (Purgative), etc. Apart from this, time of intake of drug, dose of intake and Anupana (the vehicle with which the drug may be ingested with such as hot water, milk, honey, etc.) are also emphasized in the study of herbals under Ayurveda.

In general, Ayurvedic formulations can be classified in to two categories: Kasthoushadhis (pure herbal preparations) and Rasaushadhis (herbo-mineral-metallic preparation), in which the latter contains minerals added for their therapeutic effect. However, the use of these medicines is dependent on the legislations of respective countries in regard to control of Ayurveda/Herbal/Traditional/CAM medicine. Most of the European nations allow the use of only herbal drugs and not that of metals or minerals.

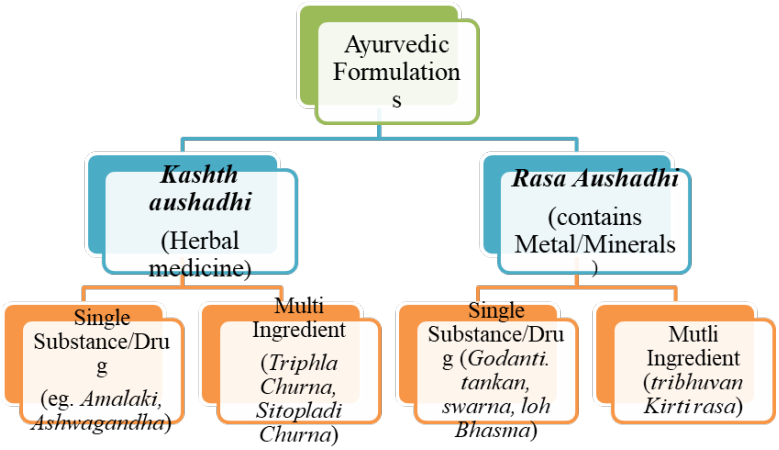

Figure 1: Classification of Ayurveda Medicines on the basis of composition

Drug formulation in Ayurveda can be classified in to two types on the basis of its composition: Single drug use and use of more than one drug in combination, in which the latter may be termed as MIC (multiple ingredient composition). The strategy of combination of drugs together in a single composition also provides extra therapeutic effectiveness.

The single drug compounds can be therapeutically used according to the chemical properties they possess. But in case MIC, the combined effect of all ingredients may be different. The MIC which are already mentioned in texts, have a proven clinical efficacy over centuries of use. Considering the aspect of developing new MIC, it becomes necessary to study the drug interactions with each other.

The phytochemical constituents present in herbals are generally present in minute quantities and sometimes are insufficient to achieve the desirable therapeutic effects. If these plants which have phytochemicals of varying potency are combined together, they may theoretically produce a greater result, as compared to solitary use of the plant. It is a positive herb-herb interaction and this phenomenon is known as synergism. Certain pharmacological actions of active constituents of herbs are significant only when potentiated by that of other plants, but not evident when used alone. The example of trikatu churna can be quoted here, where combination of ginger with black pepper, and long pepper enhances their heating and mucous-reducing effects.[5]

The Ayurvedic drugs that are mentioned in Ayurveda texts have been researched on the basis of these basic principles and which have stood the test of times in terms of their safety and efficacy, when manufactured under strict quality control. However, the advancement in science and technology and consumer awareness has mandated that Ayurveda medicines must be safe for use, efficacious and marketed in appealing packaging and easy to use form. Most of the patients may not be compliant in engulfing a powder (churna); rather he would prefer ingesting a pill or capsule of the same drug.

It is here, that the concept of preformulation studies can come to the rescue of Ayurveda pharmaceutics.

Need of preformulation studies in Ayurveda

1. Provide safe and efficacious medicines.
2. Patient compliance to certain forms of drug dosage forms like powders (churna), medicated oils (ghrita, taila).
3. To reduce the dose of certain drugs.
4. To enhance the bioavailability of drugs. E.g. Guggulu
5. To research and manufacture newer combinations.
6. To utilize the modern technology of drug manufacturing, while keeping the essence of Ayurveda principles intact.

Preformulation

Preformulation is defined as the branch of pharmaceutical science that utilizes biopharmaceutical principles in the determination of

physicochemical properties of the drug substance.[6] It refers to the study of physico-chemical properties of drugs- whether single or combined, in order to develop a safe and efficacious medicine for use. It is the first step in the rational development of dosage forms of a drug substance. It can be referred to as an investigation of physical and chemical properties of a drug substance alone and when formulated with other combinations or excipients.[7] During pre-formulation phase of product development, characterization of the drug molecule is a very important step. It also includes the determination of certain fundamental physical & chemical properties of drug like accelerated stability (stress) studies, stability-indicating analytical method development, and other physico-chemical characterization designed to pinpoint stability problems and enable formulation optimization.

Ayurveda and preformulation

The pharmaceutical sector of Ayurveda medicines is growing by leaps and bounds globally. India and China are considered as the main exporters of Ayurveda or herbal medicine. Currently, herbal formulations are processed in to end products adopting large scale technologies which are sometimes modified forms of classical method of drug manufacturing.

The approach in past decade has changed towards the extraction of pure bioactive compounds from Ayurvedic herbs and substances whose therapeutic effects are well documented in traditional texts. Since traditional Ayurvedic methods of preparing crude drugs and formulations are labour intensive, time consuming, and require validation and standardization; scientists in research and industry have opted to use modern organic solvent extraction methods to isolate bioactive components from the original plants/substances. However, the extraction and isolation of pure chemical compounds from a medicinal plant is controversial, as Ayurveda and other systems of herbal medicine have always advocated holistic healing with single/multi-herbal formulations. Indeed, empirical studies perfected over thousands of years have established stringent protocols for preparation of therapeutic Ayurvedic formulations with minimal side effects.

The advancements in pharmaceutical industry have also led to emergence of new class of drugs known as phytopharmaceuticals, where a single molecule or the principle metabolite of an herb is extracted and used as a single drug. These are technology driven processes of extraction of active metabolites from plants. In contrast, traditional processes use water, alcohol, fats, milk as an extraction medium. These offer enhanced therapeutic efficacy, are safer and provide a benefit of reduced dose thus increasing the patient compliance. Moreover, these extracts must be proven to have a history of safe use (HOSU).

Since the drugs prepared conventionally using techniques mentioned in Ayurveda texts, can be considered as a HOSU material, it is important to generate scientific data on the pharmaceutically processed material of the same herb produced industrially using modern processes. This is important as the phytopharmaceutical raw-material produced by the pharmaceutical process needs to be similar in characteristics and composition to a HOSU material and such similarity or dissimilarity data would only lead to extrapolatability of the safety profile of the HOSU material to the phytopharmaceutical.[8] This can be achieved by characterizing the material using Chromatography (TLC, HPLC) or Spectroscopy.

Once, the individual extract has been characterized and its similarity with history of safe use material has been established, preformulation studies can be undertaken. But, uunlike pre-formulation studies in a pharmaceutical based on synthetic drugs where large guidance and techniques are available, the area for herbal medicine is bereft of the same. Several aspects and measurement techniques are needed to study the properties of the phytopharmaceuticals, so as to know the ability to obtain quality solid dosage form formulations. Some of the common attributes that need to be studied and suggestions are mentioned in Table-1, although these are non-exhaustive. For other tests/protocols, reference to the various editions of Ayurvedic Pharmacopoeia of India should be considered.

Table 1: Probable Parameters for Preformulation study of Ayurveda Drugs

Organoleptic properties	Stability
Purity	Hygroscopicity
Particle size and shape	Binding properties
Solubility and dispersibility	Interaction with excipients
Drug- Drug Interaction	Concept of Incompatibility

Organoleptic properties

This includes the physical characteristics that can be examined merely by sense organs such as colour, odour, taste and touch. Colour is closely related with the composition of every material; mostly the extracts are dark brown or black in colour. Some compound have specific odour. Drugs containing sulphur may give unpleasant odour of sulphur after burning. Similarly, taste and touch are correlated with chemical nature. In case of herbo-mineral drugs, presence of metallic particles in bhasma gives specific metallic taste. Such bhasma are considered as unripe or incompletely incinerated and able to cause nausea, vomiting, gastric irritation, various skin diseases and major harm to vital organs if administered internally for longer duration.

Purity: This is another important aspect for preformulation studies. For every compound, depending on its dose and toxicity, the limit of impurity is defined. Until and unless the purity of the drug is assured other studies like stability, degradation and toxicity cannot be performed. Various parameters which are considered to find the purity of the drug substance are pesticide residue, TLC, HPLC, UV absorption, IR spectra. All poisonous herbs, highly potent drugs and all metals-minerals are advised to use only after proper purification. According to chemical point of view, Ayurvedic purification methods may result in depletion of percent purity but according to therapeutic point of view, these purification methods removes some toxins and make the metals-minerals suitable for further processing. E.g. the content of aconite is reduced in vatsnabha (*Aconitum heterophyllum*) after purification in gomutra.

Particle Size and shape: It is more important when bhasma of metals and minerals are used as drug. The bhasma have a particle size ranging from micron to Nano meters. The smaller the particle size, easy would be the dispersion, solubility and assimilation in the body.

Solubility and dispensability: The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently, the therapeutic efficacy of the pharmaceutical product. Knowledge of the extent of solubility is important to decide the need for additional steps of adjustment to get the right quantum or, need for a step of filtration during manufacture.eg. Syrups.

Stability: Before any new compound is taken up for clinical trials, stability profile of new drug substance is very much needed to proceed further to enter into product development. The

substance may have some changes due to environmental factors. It may degrade, thus decreasing its efficacy or may change to some other compound due to reaction, thus becoming unsafe for use. Thus, stability testing is the primary tool used to assess shelf life and storage conditions for pharmaceutical products. Stability studies are linked to the establishment and assurance of safety, quality and efficacy of the drug product from early phase development through the lifecycle of the drug product.

Hygroscopicity: This may be considered in stability studies. The herbal extracts are very much prone to changes in their structure due to moisture in atmosphere. They may either be hygroscopic or effervescent. It may have serious implications during the manufacturing process, environmental controls on the manufacturing, packaging, and most importantly on the stability and microbial qualities of the material and formulations.

Binding properties: The data on binding properties may give an idea about the excipients that may be used. It may also suggest the dosage form of the drug, either capsule form or tablet form.

Interaction with excipients: Though excipients are considered as inert and do not interfere in drug interaction with the body; however it is not always necessarily true. For example, in case of the phytopharmaceuticals formulated with magnesium oxide/magnesium carbonate as an anticaking agent, which may show slight "laxative effect or potentiate such effect if the phytopharmaceutical also is originally known for laxative effect."

Drug-Drug Interaction: In a MIC, the components may have a positive or negative interaction with each other. The components may be synergistic to each other and enhance the effect of each other. They may be antagonistic to each other and counteract the effect of each other.

Concept of incompatibility: One of the basic principles of Ayurveda, no two ingredients having incompatibility (Virudhha) to each other must be formulated to gather.

New combinations of different plant material should be searched and studied for their therapeutic effects also.

Suggestions for the industry

Apart from undertaking the preformulation studies, some of the outlines of which have been stated above, certain modifications in manufacturing processes can be done to improve the efficacy of drugs. The powders or extracts can be potentiated by triturating (bhavna) with decoction or juice of same drug. This potentiation can also reduce the dose of drug. The process of purification of drug should be compatible with its intended use. This can be understood by an example where gandhak (Sulphur) is intended to be used for GIT disorders; it can be purified by bhringraj swarasa instead of milk.

CONCLUSION

The industry should develop new compositions keeping the basic principles of Bhaishajya Kalpana (Ayurvedic Pharmaceutics) and chikitsa (therapeutics) in foresight. It is where the preformulation plays a major role in developing rational, safe and efficacious Ayurveda drugs. The conventional techniques of preformulation R&D may not be effective for Ayurveda drugs and there is a need to modify its structure in order to meet our expectations. A lot is known about the properties of single drugs as well as multi ingredient formulations from the ancient texts and this knowledge can be effectively utilized by the industry during the preformulation R&D. Interaction of various components in compound medications, their stability, therapeutic effectiveness and safety should be stressed upon. These studies may include both solution and solid state experiments under conditions typical for the handling, formulation, storage, dispensing and administration of a drug candidate as well as stability in presence of other excipients. In general practice, an Ayurveda prescription consists of multiple drugs which are advised to be taken after mixing together. These combinations should be studied and modified pharmaceutically to generate an effective single pill.

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