

Aspects of preformulation in *Bhasma Kalpa* (Incinerated metallic drug or medicines)

Dhirajsingh S Rajput, Rohit Gokarn, Anita Wanjari, Bharat Rathi



Abstract:

Preformulation is the stage of drug development in which the physicochemical properties are characterized by some parameters such as organoleptic properties, purity, particle size, shape and surface area, solubility, temperature, pH, co-solvency, solid dispersion, crystal properties, polymorphism, preformulation stability studies, pKa determination (Dissolution constant), partition coefficient, Chemical stability profile etc. *Bhasma* (Incinerated metallic drugs or medicines) are highly potent formulations frequently used in Ayurveda. In the context of *Bhasma*, Ayurveda has mentioned many parameters such as *Varitaratva*, *Rekhapurnatva*, *Apunarbhava*, *Niruttha*, *Niswadu* etc which are equivalent to some physicochemical testing parameters described in modern science. To ensure the safety and efficacy profile of these formulations is the need of hour to know their physic-chemical properties with respect to both Ayurvedic and modern tests such as *Apunarbhav*, *Niruttha*, *Varitar*, TGA, FTIR, XRD, ICP-AES etc. In present work an attempt has been made to study the significance of preformulation studies and co-relation between various parameters mentioned in Ayurveda and modern science with special reference to *Bhasma*. The review indicates that Ayurvedic testing parameters can be correlated with modern testing parameters and establishing their correlation will create a new path for understanding pharmacokinetics and pharmacodynamics of Ayurvedic medicines as well as in developing advanced dosage forms. It is clear from the review that Ayurvedic testing methods are preliminary tests before utilizing *Bhasma* for therapeutic purposes and advanced analytical techniques can be utilized for standardization, characterization and for accessing safety and efficacy of Ayurvedic medicines.

Key words: Preformulation, Ayurveda, *Bhasma*

Introduction:

Preformulation is branch of pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance [1]. It is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients [2]. During pre-formulation phase of product development, characterization of the drug molecule is very important step. Prior to the development of any dosage form of new drug, it is essential that certain fundamental physical & chemical properties of drug

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Corresponding Author:

Dhirajsingh S Rajput, Asst. Prof,
Dept of Rasashastra and Bhaishajya
Kalpana, MGACH & RC, Salod (H),
Wardha (MH)

Email: dhiraj.ayu@gmail.com

Co-author (s):

Rohit Gokarn, Asst. Prof, RSBK
Anita Wanjari, Aso. Prof, RSBK
Bharat Rathi, Prof, RSBK

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should be determined. Preformulation studies generally include accelerated stability (stress) studies, stability-indicating analytical method development, and other physico-chemical characterization designed to pinpoint stability problems and enable formulation optimization. Characterization of drug molecule is a very important step at the preformulation phase of product development [3]. In preformulation, relevant physico-chemical properties of drug substances are determined, for example solubility and stability that is important criteria to select the right substances for development. After oral administration, only the substances with sufficient solubility can be absorbed by the digestive tract and into the body, where they become effective. Stability is important, as a drug substance must remain stable during handling, formulation, storage and administration of the drug product [4].

It is clearly understood that ancient seers of Ayurveda were well aware of preformulation studies. In spite of lack of advanced instruments, they have established many simple but valuable parameters to test raw materials, prepared formulations, their shelf life and therapeutic properties. This is evident from Ayurvedic literature that such guidelines are predominantly described in detail in context of Rasoushadhis (herbo-metallic preparations). As metals are indigestible in their natural form and need to be converted into suitable digestible and absorbable form before administration hence great care was taken while preparing metallic formulations which are clearly highlighted in *Bhasma Kalpa* (Incinerated metallic formulations). These dosage forms are highly effective even at minimal dose.

Material and methods:-

The co-relation, limitations and advantages of preformulation parameters and Ayurvedic parameters with special reference to *Bhasma Kalpa* can be discussed based on following points.

- 1) Organoleptic properties
- 2) Purity
- 3) Particle size, shape and surface area
- 4) Solubility
- 5) Temperature, pH and solid dispersion system
- 6) Crystal Properties and Polymorphism
- 7) Preformulation stability studies
- 8) pKa determination (Dissolution constant)
- 9) Partition coefficient

Observation and results:-

Organoleptic properties: This includes the characteristics which can be examined merely by sense organs such as color, odor, taste and touch. Color is closely related with the chemical composition of every element i.e. crystal structure [5]. Although, different compounds may have similar color and vice versa. Diamond, graphite and coal have only carbon atoms but are different in color and physico-chemical properties [6]. Cinnabar and *Rasasindoor* have same red color but they are too showing difference in color and physico-chemical properties. Such exemptions are countable and hence color is important to identify various compounds. Some compound have specific odor although *Bhasma* do not have any odor but their odor can be sensed only after subjecting in fire. *Bhasma* prepared with sulfur gives unpleasant odor of sulfur after burning. Similarly, taste and touch are correlated with chemical nature. 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. Hence *Niswadu* test is mentioned for *Bhasma* which means tastelessness.

Purity: The purity of drug substance plays the most significant role in all studies carried out on it. For every new 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 [7]. Various parameters which are considered to find the purity of the drug substance, are melting point, UV absorption, IR spectra, TLC. Now a day these are used for identification and quantification of impurities, which are often very closely related in structure to the main compound of interest. Ayurveda consider every metal as impure in its natural state and prefer its purification before using it for therapeutic purpose [8]. 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. Thus the concept of purity is not completely applicable to Ayurvedic mineralo-metallic preparations as Ayurvedic definition of purification (*Shodhan*) is related with removal of unwanted properties, making metal/mineral suitable for assimilation in body and making suitable for *Bhasma* preparation rather than attaining pure molecules of same element. For this, Ayurvedic criteria mentioned for selecting drugs i.e. *Grahyagrahyatva* and characteristics after *Shodhana* can be considered as parameters.

Particle size, shape and surface area: Bulk flow, formulation homogeneity and surface-area controlled processes such as dissolution and chemical reactivity are directly affected by size, shape and surface morphology of the drug particles [9]. In general, each new drug candidate should be tested during preformulation with the smallest particle size as is practical to facilitate preparation of homogeneous samples and maximize the drug's surface area for interactions.

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes.¹⁰ The effect is not only on the physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. *Bhasma Parikshas* such as *Varitaratva* (particles of *bhasma* should float when sprinkled on the surface of water), *Rekhapurnatva* (particles of *bhasma* should have micro-fineness to fit into the lines of the hand and should not glitter) *Apunarbhav* (*bhasma* should not regain its metallic nature after intense heating) and *Unnam* (they should be able to take the weight of a rice grain) are related with particle size, shape and surface area. It is clear that *Varitar Bhasma* can be achieved only after obtaining desired fine particle size having specific surface area. Finer the particle size more will be absorption of drug and hence more will be bio-availability of *bhasma*. This fact suggests the importance of *Varitar* test. Today with advancement in the instrumental technologies, more reliable tests are accessible such as XRD, ICE-AES, XRF etc. these tests are time consuming, costly and leads to many difficulties to practitioners of Ayurveda. Hence it is advisable to perform *Varitar*, *Rekhapurna* and *Unnam* test before utilizing *Bhasma* in clinical practice.

Solubility: 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 [11]. Solubility of a molecule in various solvents is determined as a first step. This information is valuable in developing a formulation. Solubility is usually determined in a variety of commonly used solvents and some oils if the molecule is lipophilic [12]. Common solvents used for solubility determination are: water, polyethylene Glycols, propylene Glycol, glycerin, sorbitol, ethyl alcohol, methanol, benzyl alcohol, isopropyl alcohol, tweens, polysorbates, castor oil, peanut oil, sesame oil, buffers at various pHs etc [13]. Solubility data of *Bhasma* is not available yet and any classical test cant be correlated with accessing solubility of *Bhasma*. Advanced research regarding the solubility of *Bhasma* with specific vehicle is expected as all *Bhasma* are mentioned to be administered with specific vehicle.

Temperature, pH and solid dispersion system: Factor effecting chemical stability critical in rational dosage form design include temperature, pH and dosage form diluents [14]. Solubility of a solute in a solvent is dependent on temperature, nature of solute and nature of solvent. For some substances, an increase in temperature results in an increase in solubility [15]. *Bhasmas* are the product of repeated incineration cycles which involve repeatedly subjecting metallic particles to high temperature. Hence the possibility of significantly affecting environmental temperature changes to chemical properties of *Bhasma* is negligible provided that *Bhasma* should be stored in airtight glass bottles. Although many Ayurvedic formulations contain *Bhasma* in combined form with herbal powders which are prone to changes in temperature. It is difficult to interpret effect of change in temperature on *Bhasma* or *Bhasma* containing formulations. Research is needed to establish association between temperature changes and chemical properties of *Bhasma*.

Weak electrolytes undergo ionization and are more soluble when in ionized form [16]. The degree of ionization depends on dissociation constant (pKa) and the pH of the medium. If the substance is brought outside its pKa, i.e. the pH value where half the substance is ionized and half is not, then solubility

will be changed because it leads to introducing new intermolecular forces, mainly ionic attraction. *Bhavana* (levigation with herbal juice) is an important procedure performed in pharmaceuticals of Ayurveda. While preparing *Bhasma*, repeated *Bhavana* of specific herbal juice such as *Alo vera* juice, lemon juice etc are performed which help in impregnating organic molecules in metallic particles. This effect has elaborated by using FTIR studies.

Solid dispersion system can be determined by thermal analysis, x-ray diffraction method, microscopic method, spectroscopic method, thin layer chromatography and solubility determination. Thermal analysis is used to study the physico-chemical interactions of two or more components. X-ray diffraction method helps to know chemical composition and structural arrangement of compound [17]. Microscopic method has been used to study polymorphism and morphology of solid dispersion. In spectroscopic method, the spectra of pure drug and the dispersed drug are scanned. In thin layer chromatography characteristics of pure and dispersed drugs are studied to test whether the drugs are decomposed by process. Solubility determination results from aqueous solubility studies of drug in various concentrations of carrier would indicate interactions between drug and carrier [18]. Thus dispersion system is applied to obtain a homogenous distribution of small amount of drugs at solid state, to stabilize unstable drugs, to dispense liquid or gaseous compounds, to formulate a faster release priming dose in a sustained release dosage form and to formulate sustained release dosage or prolonged release regimens of soluble drugs by using poorly soluble or insoluble carriers. Solid dispersion system is an advanced technology which should be applied to study pharmacokinetics and pharmacodynamics of *Bhasma* with different vehicles, after levigating with different herbal juice and in combination with other herbal drugs.

Crystal properties and polymorphism: Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism [19]. Polymorphs generally have different melting points, x-ray diffraction patterns, and solubilities, even though they are chemically identical. Differences in the dissolution rates and solubilities of different polymorphic forms of a given drug are very commonly observed. When the

absorption of a drug in dissolution rate is limited, a more soluble and faster-dissolving form may be utilized to improve the rate and extent of bioavailability [20]. Various techniques are available for the investigation of the solid state. These include microscopy (including hot-stage microscopy), infrared spectrophotometry, single-crystal X-ray and X-ray powder diffraction, thermal analysis, and dilatometry. It is interesting to mention that in classical texts, there are many methods mentioned to prepare *Bhasma* of single metal/mineral which may create their polymorphic forms. It can't be neglected that different batches of *Bhasma* prepared by adopting similar method can also create different polymorphic forms as the materials utilized for purification and herbal juice for *Bhavana* may slightly differ in chemical composition. The pressure applied during *Bhavana* may have direct effect on space lattice arrangements. Variation in the physico-chemical properties of herbs with respect to seasonal and geographical changes is another reason which may create different polymorphic forms of *Bhasma*. Hence elaborating best form of particular *Bhasma* among its various polymorphic forms will be valuable contribution in the development of Ayurveda.

Preformulation stability studies:- The drug substance characterization and stability is usually determined as part of preformulation studies. 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, as stability testing is the primary tool used to assess expiration dating and storage conditions for pharmaceutical products [21]. 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. Regarding *Bhasma* classical texts have narrated that *Asava-Arishta*, *Dhatubhasma* and *Rasabhasma* didn't have expiry dates and much older the formulation better will be its potency and efficacy. It seems that the mentioned classical claim have some limitations as *bhasma* are the product of metals/minerals which mostly have tendency to react with environmental humidity, oxygen from air and can be contaminated if not handled properly (e.g. *Tanmra bhasma*, *Kasisa bhasma*, *Swarnamakshika bhasma* etc). Hence *Bhasma* are stored in airtight, amber

colored glass bottles. Attempt can be made to scientifically elaborate the classical claim.

pKa determination (Dissolution constant): For a compound containing basic or acidic functional groups, solubility at a given pH is influenced by the compound's ionization characteristics. The solubility of a compound in aqueous media is greater in the ionized state than in the neutral state [22]. Thus, solubility of ionizable compounds is dependent on the pH of the solution. Determination of the dissociation constant for *Bhasma* capable of ionization within a pH range of 1 to 10 is important since solubility and consequently absorption, can be altered by orders of magnitude with changing pH.

Partition coefficient: Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium [23]. Drugs having values of partition coefficient much greater than one are classified as lipophilic, whereas those with partition coefficients much less than one are indicative of a hydrophilic drug [24]. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate, pKa, and solubility on absorption must not be neglected. For Ayurvedic medicines especially *Bhasma*, partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption [25]. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/hydrophilic nature of the drug. Since biological membranes are lipoidal in nature, the rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule.

Discussion:-

Every medical science has its own view regarding preparation of medicine and method of its utilization. The awareness towards safety and efficacy of medicines has been increasing which resulted in discovery of more and more advanced methods of testing medicines. Rapid augmentation in industrialization of medical pharmaceuticals is playing

major role in increasing the significance of preformulation studies. It is understood that seeds of science of preformulation studies were planted far before the origin of medical science as separate branch. In classical texts of Ayurveda, description of acceptable good qualities of herbs, metals, minerals, their types, and effect on body both in impure, purified and processed form represent moderate development of preformulation studies. Ayurveda is science of life and centered on therapeutic aspect. This may be a reason why the properties of all drugs in Ayurveda are narrated upto therapeutic point of view and very little attention is given towards chemical properties. However there are many similarities between the preformulation parameters and Ayurvedic perception in the context of medicinal preparations such as *Bhasma*.

Preformulation parameters such as purity, particle size, shape and surface area, solubility, temperature, pH and solid dispersion system, crystal properties and polymorphism have common association with classical tests which has been discussed earlier. However the parameters such as preformulation stability studies, pka determination (dissolution constant), partition coefficient etc have their unique importance and should be applied for research on Ayurvedic medicines specially *Bhasma* and *Bhasma* containing formulations (herbo-metallic formulations). Conducting research on *Bhasma* and herbo-metallic formulations is a very difficult task as there are hundreds of methods for preparation of single *Bhasma* and over 10,000 herbo-metallic formulations. The central authorities of Indian system of medicine and many Ayurvedic institutes are engaged in research and development of Ayurvedic medicines. Hope so, present work may prove a torch bearer for preformulation studies of Ayurvedic medicines.

Conclusions: Preformulation stability studies are usually the first quantitative assessment of accessing physico-chemical properties of a new drug. These studies 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. Ayurvedic seers have also performed preformulation studies to maintain

safety and efficacy of medicinal formulations. Ayurvedic methods are simple and enough informative to access safety and efficacy but insufficient to provide complete information of physico-chemical properties of *Bhasma*. It is advisable to use Ayurvedic tests as preliminary tests before utilizing *Bhasma* for therapeutic purposes and advanced analytical techniques can be utilized for research and development of new dosage forms.

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