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Some observations on the metal-based preparations in the Indian Systems of Medicine

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The real physicochemical nature of the classical metal preparations, the *bhasmas* in the Indian Systems of Medicine (ISM) is not very clear. Of late, doubts have been raised as to their utility and suitability as medicine. The *bhasmas* are in fact products of classical alchemy - inorganic compounds of certain metals and gems in a very fine powdered form, mostly oxides, made in elaborate calcination processes perfected several centuries ago. For most of the metals, methods of *bhasma* preparation as given in the classical texts differ between themselves in terms of accompaniments and process detail. Correspondingly, the processing of a certain metal lead to *bhasmas* with different colours. The resultants are considered to be the same medicinal substance with the ascribed indications even though these may differ in composition between them and should ideally be addressing different ailments. In short, there is no standard *bhasma* of a metal as such. In view of such ambiguity and the risks attendant to their inconsiderate use, there is an urgent need to bring about a standardization of these preparations- process and the end product, as also to resolve the respective indications and strengthen the regime to monitor the manufacturing, and administration of these preparations.

Keywords: Indian Systems of Medicine, *Bhasma*, Safety issues, Drug Standardization

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In the recent times, public interest the world over has shifted towards traditional medicine for safety concerns, namely, about the occasional adverse reactions and side effects that entail usage of many an allopathic formulation. In India, Traditional Systems of Medicine consist mainly of *Ayurveda, Unani* and *Siddha*. The medicines made under these systems use drug material of plant, mineral and animal origin which is well documented in the traditional and scientific literature for their healing properties. These systems are very similar in terms of the drug material used that is mostly common among them. Amongst these systems, some differences in the process of making medicine and, the philosophy of treatment are there. Any reference to *Ayurveda* here should therefore be regarded as encompassing. Being used over a long period, these medicines are acknowledged as safe. However, the use of metallic preparations as single drugs or as ingredients in many an *Ayurvedic* medicine has evoked concern and debate in the scientific and public forums in the recent times. Ayurvedic practitioners (*Vaidyas*) have been agitated over recent reports expressing serious concerns about ISM formulations having the so called heavy metals[1]. Concentrations (μg/gm) of lead, mercury, and arsenic in various medicines were measured by x-ray fluorescence spectroscopy. Estimates of daily metal ingestion for adults and children using manufacturers' dosage recommendations were compared to US Pharmacopoeia and US Environmental Protection Agency regulatory standards. It was found that one of 5 Ayurvedic medicines produced in South Asia and available in Boston South Asian grocery stores contains potentially harmful levels of lead, mercury, and/or arsenic. The study warned that users of *Ayurvedic* medicine may be at risk for heavy metal toxicity, and suggested that testing of *Ayurvedic* medicines for toxic heavy metals should be mandatory. Many experts dwelling upon the authority of classical texts as handed down the ages have refuted ill effects of heavy metals on the human body. Their contention is that the so called heavy metals were not heavy on the human body and that *Ayurvedic* medicines containing heavy metals (used in the form of *bhasmas*) were completely safe to use. In the paper, attempt has been made to decipher the heavy metal

compounds that form part of the ISM medicines as an ingredient, i.e. *bhasmas* of metals and certain minerals, as substance and as medicine. These are basically inorganic metal compounds only and there is no standard *bhasma* of a metal as such. Their identities and actions need to be very clear to the practitioners because an inconsiderate use can cause episodes of adverse drug reactions. Results of some relevant work to put the *bhasmas* in a wider perspective and need for further research have been discussed.

Heavy metals: elements vs. the *Bhasmas*

Medicines under the Indian Systems of Medicine (ISM) are required to be manufactured in sanitized environs following Good Manufacturing Practices (GMP) norms, duly laid down by the Government of India. The Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) is the regulator of the ISM manufacture in the country[2]. Among other things, AYUSH is involved in evolving pharmacopoeial standards for Indian Systems of Medicine and Homoeopathy drugs. Some time ago, AYUSH has issued new notifications as also various amendments pertaining to heavy metal contents, shelf life, labeling systems and approved drugs' centralized registration for achieving qualitative standards of ISM drugs and formulations. AYUSH has also set the limits on the concentration of heavy metals in particular (Table 1). The ISM medicines must pass the laboratory tests for these limits and carry the phrase *Heavy metals within permissible limits* on their labels for plant and animal drugs but not mineral drugs. The heavy metals listed are most often implicated in accidental human poisoning. Heavy metal poisoning is the toxic accumulation of heavy metals in the soft tissues of the body. A heavy metal is one with a specific gravity of 5 gm cm^{-3} or more. They are stable elements and cannot be metabolized by the body. It may be noted that some heavy metals, such as zinc, copper, cobalt, chromium, iron, and manganese are required by the body in small measures, but these same elements can be toxic in larger quantities. Heavy metals may enter the body in food, water, or air, or by absorption through the skin. Once in the body, they compete with and displace essential minerals such as zinc, copper, magnesium, and calcium, and interfere with the functioning of the organ system.

Table 1—The toxic metals and the permissible limits

Heavy metals	WHO & FDA limits
Arsenic (As)	10 parts per million
Mercury (Hg)	1 ppm
Lead (Pb)	10 ppm
Cadmium (Cd)	0.3 ppm

The most important concern about heavy or toxic metals in the *bhasmas* is whether the human body retains or expels them, and how well. The *Ayurvedic* practitioners assert that one must treat discretely the heavy or toxic metals in elemental form-*read* toxic, from those in compound form-the *bhasma*, regarded human-safe[3]. *Bhasmas* are made from metals like zinc, lead, gold, silver, tin, copper, metal mixtures and alloys as also from gems, coral and mica and some other minerals, etc. These are formed by calcination of the parent substance (metal or mineral), singly or in combination with other substances like minerals, etc. in a rigorous, prescribed manner after it has been appropriately purified and emasculated with herbal juices or minerals. There are several traditional texts that a *vaidya* can refer to for preparation of a *bhasma*. A comprehensive account is available in several standard texts[4,5]. The *bhasmas* are in a very fine powdered form and have to be administered orally in small quantities, sometimes as single drugs in appropriate vehicle. These are considered very potent and are acknowledged with power to address a large number of chronic ailments. *Bhasmas* treated and prepared only with herbal juices are considered milder in nature compared to those prepared with white arsenic or mercury, etc. A *vaidya* first determines the constitution of his patient and takes into account the disease history before prescribing a particular *bhasma*. A great emphasis is laid on dosage and the *anupana* (vehicle) such as milk, butter and honey, etc. with which a *bhasma* should be administered. In the *anupana* may possibly lay the key to the safety aspect of a *bhasma.* In the absence of such caution, adverse drug reaction is likely.

At this juncture, it will be relevant to look very briefly at the history of use of metal compounds in the Indian medicines. *Ayurveda*, whose origins date back to the *vedic* period, evolved over the centuries into a comprehensive and rational medical system with a strong preference for plant based remedies[6-8]. *Rigveda* and *Atharvaveda* contain recounts of medicine. The oldest surviving written treatises are those of *Bhela, Caraka* and *Susruta*, which refer to 8 different branches of medical knowledge, namely, therapeutics (*kayachikitsa*), surgery (*shalyatantra*), ailments

related to ear nose throat, etc. (*shalakyatantra*), mental ailments (*bhootvidya*), pediatrics (*kumarbhrtya*), toxicology (*agadatantra*), restorative treatment (*rasayana*) and virilifics (*vajikaranatantra*). The last two branches invoke certain specific processes, and drug materials like herbs, metals and minerals as rejuvenators. Of particular interest here is *rasachikitsa*, rather extraneous to *Ayurveda* and evolved by the so called *Siddhas*, which invoked only metals, alloys and their compounds and salts as also sulfur as its drug materials. While the first use of compounds of mercury in medicine is found in the *Susruta Samhita* (300-400 AD), their omnipotence, as also of gold in all kinds of ailments and even all phases of life was first propounded in the *Tantric* texts. With time, inorganic substances were increasingly incorporated into the *Ayurvedic* Materia Medica. This came to be as a result of extensive work of generations of alchemists. The new materials were manmade-obtained from minerals and ores in chemical or metallurgical processes employing elaborate equipment devised for the purpose. How did this differ from alchemy whose sole aim was to find the magic substance that would transmute base metals like lead, tin, mercury and copper into the noble ones (gold and silver) and prepare the Elixir of Life for immortality? The aim of *Ayurveda* was nobler and as a wholesome system it stressed on therapeutic procedures and rejuvenation. Alchemy (*rasavidya*) prospered in India during the 9^{th}-18^{th} century in the hands of the *rasavadins* (alchemists). It came to be in full vigour during the period 10^{th}-14^{th} century. The Indian alchemical texts (the *rasashastras*) of even the 11^{th}-12^{th} century refer to many compositions to be used as medicine for treating specific ailments. Mercury was a wonder substance to them. It was center stage as the king of *rasas*- one that will bring happiness and prosperity. They developed a great expertise in the preparation of a number of compounds of mercury and also converting a number of minerals into what is known as *bhasma*. The *bhasmas* date as far back as the 8^{th} century and Nagarjuna is credited as the foremost authority on these preparations. All of this is well before the times of Lavoisier when, in the 1770s, he perfected the art of calcination of metals to subvert the grand old ideas of chemistry and revolutionize it. Curiously, metals and minerals have been part of European pharmacology since the Renaissance (14^{th}-7^{th} century) when Paracelsus (1490-1541) because of his alchemical training introduced the use of metals like mercury, arsenic, tin, lead and antimony - all toxic, in the medical practice which were believed to give perfect health and cure all diseases.

The *bhasmas* have always enjoyed a mystical preponderance in the ISM. A large number of these are attributed with aphrodisiacal properties that suggest them to be rather scrupulous substances. Precious metals and gems have always fascinated mankind. As rare and exotic substances, these have tremendous psychological pull. It is therefore not just coincidental that many of them were used to make their *bhasmas*, attributed with superior healing powers. In reality, most gemstones are composed of common elements and substances like carbon, silica, alumina and lime, etc. Their distinctness lies in how the elements combine and crystallize. Alchemy and *rasachikitsa* flourished together as mutual sustenance was possible. It gradually faded by the 1800 AD. Metallurgical developments after this period are not incorporated into the texts[8]. However, the specific equipment and metallurgies evolved by the practitioners of the times have great scientific merit and should be of interest to the specialists of material sciences and of chemistry alike.

What is the chemical nature of the end product of the *bhasma* process? This is seldom ever stated in the texts. The monographs published by the CCRAS and CCRUM specify the elements but do not identify the substances or the drug intermediates[9-12]. In calcination, a metal is heated to a high temperature in a kiln below its melting point in an inadequate supply of air when it undergoes thermal decomposition or a phase transition other than melting. As a result, the metal becomes friable and may undergo oxidation or reduction. The entire process of *bhasma* is thus one of producing a salt of the metal, mostly an oxide. The hearth preparation is an elaborate one and is of various sizes. The hearths would generate different peak temperatures as also handle varying batch sizes. The scope for regulation of conditions is limited. However, that is fine with the *vaidya* as he does not really need a precise estimation of any physical parameters other than the hearth dimensions, the number of cow-dung cakes as fuel and quantitative measures of the various substances used in the course of the process. The *bhasma* process might have to be done several times over. The temperatures reached, specific to a *bhasma* or the hearth, are not available but should be very high indeed. There is a

very indirect reference to a wide range, namely, 200°-1,200°C (hereinafter ASS); for *swarna* (gold) *bhasma*, *yashada* (zinc*) bhasma*[13-15]. One can well imagine what happens at these temperatures to the herbal juices or carbonaceous substances the metal has been treated with before or during the process. A properly made *bhasma* should neither have any metal remnants, however fine, nor any carbonaceous matter. Any organic matter or minuscule organic compound the metal may presumably have formed will suffer thermal decomposition as it might not survive the high temperatures. In the *bhasma* process, the metals and gems are assimilated not only with herbal juices, but also with substances like mercury, sulfur, arsenic oxide, arsenic sulfide, rock salt, etc. The number of iterations can differ, the more the better. Many metals undergo a large number of calcinations, for instance, 7 for tin, up to 21 for silver, 10-12 for gold and 21 to 1,000 for iron. The iterations are undertaken according to a well laid out procedure of treating the substance of calcination. With a calcination a day, the *bhasma* management would be a complex process ranging from preparations to meticulous documentation, all manual. For a thousand iterations, it will see the light of the day more than three years later. So, either a *bhasma* must be ready in advance or the patient must wait for some time before he can be administered with it.

One of the classical tests of a well prepared *bhasma* is that its particles will float on water, due to surface tension of the latter. The metals are methodically reduced to as small pieces as possible and crushed before the process. Initially, the *bhasma* particles have a wide range in size distribution. But in successive calcinations, much smaller particle sizes are reached and the range gets narrower. Eventually, the particle sizes reach colloidal scales (from a few microns to a few nanometres). Some recent studies of the microstructure of *yashada* (Zn), *vanga* (Sn) and *rajata* (Ag) *bhasma* have been revealing[15-17]. These measurements indicate that the particle sizes approach as low as 10-15 nm and stabilize to a narrow range. *Bhasmas* are thus nanoparticles. These sizes imply high surface to volume ratio of the particles that translate into better absorptivity, and so, effective drug delivery. One must appreciate the elaborate techniques developed by the *rasavadins* to cleanse parent drug material and achieve extremely fine particle sizes in numerous iterations of the process. The realization that fine particle sizes attribute high potencies and effective reach to the *bhasmas* must have been a result of a series of experimentation and observations spread over long periods of time. The *vaidyas* contend that the *bhasmas* have no expiry if stored properly. AYUSH has fixed 5 yrs to the expiry of a *bhasma* from the date of its manufacture. As we shall see later, this needs qualification. An x-ray fluorescence spectroscopy study of the *bhasmas* of copper, iron and lead revealed strong presence of these elements and oxygen[18]. There were some other elements present but in traces only, except in the case of copper where sulfur was present in a large proportion. This is because of its having been used as a calcination accompaniment to copper. The *mandur bhasma* showed up with some silicon. Knowing where *mandur* (iron rust) is obtained from, this is explainable as contamination with soil. Impurities in traces come from accompaniments and the containers themselves.

The *bhasmas* of metals are inorganic compounds, several identifiable as simple oxides. It is not known if any organometallic complex molecules are also formed in the process. Their proportion in the end product is only minuscule. A chemical analysis of *yashada* (zinc) *bhasma,* a brown coloured powder, obtained from a reputed manufacturer in Uttar Pradesh by the Bangalore Test House in 2000 revealed it to be 87.31% zinc oxide (ZnO), 0.5% potassium. This should actually be a drug intermediate. It is not known what other drug materials were used as accompaniments in the process. The laboratory did the assay only for ZnO what it was asked to. It should be borne in mind that in each cycle of calcination the oxidation process would progress in a different way as the composition of the substance in question changes. Thus, had the *bhasma* process been extended with some further cycles, it would have led to the desired, pure ZnO. For zinc, 10-11 incinerations are prescribed. The *vaidya* who makes or the practitioner who administers such a *bhasma* is unmindful of the identity and quantities of the impurity present therein, leave aside its pharmacological implications. Of these, the most serious is the one of the likely presence of fine metal particles. Laboratory assays done on the *bhasmas* generally identify only the elements present. Information on the chemical nature and pharmacological action of the drug intermediates is very crucial but is not available to the practitioner.

A correspondence between a few metal *bhasmas* and oxides and sulfides of the same metals has been drawn (Table 2). Some basic information from standard texts with additional information from other references and laboratory test reports of a few *bhasmas*, courtesy the Bangalore Test House (BTH), Bangalore is taken[4,5,13,19,20]. The correspondence is illustrative but enables us to draw some inferences. A plurality of *bhasmas* of some metals has been noticed. This is not surprising since for a given metal a text gives more than one method to make its *bhasma* while treated respectively with different drug materials. The resulting *bhasmas* show up with different colours. Consequently, these will have different physical and chemical characteristics. This can come about due to any of the following or some combination among them such as formation of oxides where a metal takes on different valence states; these compounds have different crystal structure and physical and chemical properties; compounds formed by the metal with the accompaniments, and, drug intermediates; doping of the *bhasma* crystals with impurities (foreign atoms) present even in very minute proportions; in doping foreign metal atoms substitute in the structure of a crystal for atoms of similar size; for example, the zinc oxide can be doped with aluminum, copper, and silver at dopant levels ranging from several ppm to several percent; polymorphism; ZnO, e.g. is a polymorphic substance; when heated ZnO turns yellow but returns to its white colour after cooling down; many crystals which are polymorphic show this property; polymorphic substances are chemically the same but, importantly, can have different physical and chemical properties due to different intrinsic energies of the crystals; the polymorphs produce different pharmacological actions with one form faring better in terms of solubility and bioavailability, etc.; *bhasmas* of metal mixtures and alloys will contain variably mixed compounds depending upon the relative proportions of the elements and the accompaniments[23].

For nearly all the metals, the methods of *bhasma* preparation differ among the texts themselves[13,19,21,24]. The differences are not just in terms of the accompaniments of a metal. Peak temperatures reached and exposure span in each cycle differ too, leading to oxide variants. The other crucial issue here is that of oxide stability. All metal oxides begin to form their respective carbonates as they get exposed to carbon dioxide in the environs (25% + humidity) or even in our exhaling onto some. Gold oxides are unstable compounds: aurous oxide easily reduces to the gold metal and oxygen; auric oxide is relatively the more stable one. Stannous compounds are also readily oxidized to the more stable stannic state, whereas the plumbous compounds are much more stable than their tetravalent plumbic counterparts[20]. The compounds formed by metals taking on different valence states should be treated as distinct *bhasmas*, addressing different ailments. However, the indications attributed to such *bhasmas* in the texts are wide spectrum and not resolved. This is non-trivial. The indications should be resolved through extensive clinical studies. Such studies together with the possibility of externally controlling the production of a desired polymorph form (crystal engineering) can in turn prove very fruitful. Further, the less stable ones should be accorded a shorter shelf life. Alternatively, these may need suitable stabilization or packing specifications.

A common chemical form among some of the *bhasmas* was also noticed. First, consider *the loha* (iron) *bhasmas,* namely*, kasis bhasma, mandur bhasma, lauha bhasma, vimal bhasma* and *faulad bhasma*. All of these are red in colour. *Kasis* (green vitriol) is ferrous sulfate ($FeSO_4.7H_2O$) that gives ferric oxide (Fe_2O_3) upon heating. *Mandur* is iron rust, the hydrated oxide of iron ($2Fe_2O_3.3H_2O$). It should preferably be over 100 yrs old; a misconception here is that as it ages it becomes enriched with oxygen. *Vimal* is marcasite (FeS_2); when heated in air, it gives Fe_2O_3. *Faulad* (steel) is an alloy of iron, with carbon (0.5-1.5%) and some other elements in traces. In their pure form, free of any carbonaceous matter or raw metal particles*, kasis, mandur, lauha, vimal* and *faulad bhasma* are ferric oxide only. Thus, these do not have to be treated as different entities. These are, and surprisingly, certain indications differ. This could be partly due to choice in the vehicle or accompaniment of administration. A similar case is with the *prawala* (calcium) *bhasmas*, namely those of *mukta* (pearl), *prawala* (coral), *shukti* (oyster), *shankha* (conch) and *varatika* (*kapardika*, marine shell). Used as a medicinal substance, these are all essentially calcium carbonate only. $CaCO_3$ has a melting point of 825˚C; it decomposes upon heating at this temperature producing corrosive fumes of calcium oxide (CaO) that reacts with acids, aluminium and ammonium salts. *Mukta* (pearl) is 82-86% calcium carbonate with about 10-14%

Table 2—A correspondence between *bhasmas* and oxides of a few metals

Metals	*Bhasma* colour	Corresponding metal compound	Compound colour	Remarks
Lauha (Iron)	Red dark brown (BTH)	Ferric oxide (Fe_2O_3)	Red	A dark violet one; with cinnabar, the resultant obtained is black in colour; dark brown (BTH)[13.] (Ferrous oxide FeO and ferroso-ferric oxide, Fe_3O_4 are black.
Naga (Lead)	Light red	Lead oxide (Pb_3O_4)	Light red	Red lead, Pb_3O_4 is a compound oxide ($2PbO.PbO_2$); it is not for internal use; it is harmful if inhaled or swallowed; it may cause harm to the unborn child or impair fertility. The *naga* bhasma has several variants: black, white, yellow, red and green, made using different accompany- ments[21]; these may differ from each other in composition. Plumbous oxide (PbO) is yellow, lead sulfide (PbS) is black, plumbic oxide is purple brown; no other simple inorganic compound of lead is green except pyromorphite (lead chlorophosphate: $Pb_5(PO_4)_3Cl$), a mineral green, yellow and brown in colour. Litharge - PbO is not for internal use; it may cause reproductive disorders; PbO is harmful by inhalation, ingestion and through skin contact. PbO_2 is a strong oxidizer giving off oxygen and PbO; may be fatal if swallowed or inhaled; a neurotoxin). PbO is dimorphous, in yellow and red form.
Rajata (silver)	Black	Argentous oxide (Ag_2O), argentic oxide (AgO), argentic sulfide (AgS)	Black brown; grey; black	The *bhasma* is mentioned as silver oxide[14]; silver is processed with cinnabar and the *bhasma* is a sulfide, not oxide; it is done with orpiment. CCRUM monograph mentions the *Kushta-e-Nuqra* (silver) as grey in colour whereas the RSS mentions a dull red colour.
Swarna (Gold)	Violet; red	Aurous oxide (Au_2O), Auric oxide (Au_2O_3)	Greyish-violet; red or brown	Two *swarna bhasmas* with colours as above, the violet one from gold with arsenic and sulfur and the red one with mercury[13]; a white *bhasma* also[21].
Tamra (Copper)	Black	Cupric oxide (CuO); cupric sulfide (CuS)	Black; black; (in contrast, Cu_2O is red in colour)	*Bhasma* may also contain cupric sulfide, also black; this is because sulfur is an accompaniment to the metal in the processing. The RSS mentions a blue one also. CuO is harmful if swallowed. It affects the liver and the kidneys. It causes irritation to skin, eyes and respiratory tract. Cu_2O is relatively less severe.
Trivanga (Lead, tin & zinc in a 1:1:1 ratio)	Pale yellow; white	Plumbous oxide (PbO), stannic oxide (SnO_2), zinc oxide (ZnO),	Yellow, white, white	The RSS gives a method where sulfur is not used. (Stannic sulfide SnS_2 and zinc sulfide are yellow).
Vanga (Tin)	Greyish-white, white	Stannic oxide (SnO_2)	White	SnO_2 is skin, eye and respiratory irritant. Stannous oxide (SnO) is grey; it oxidizes readily to a more stable SnO_2 when heated in air. Stannous sulfide SnS is brown-black or grey. *Bhasma* is identified as SnO_2, white in colour. The *bhasma* crystals are tetragonal, just as in the mineral casserite (SnO_2). A BTH test report identifies the *bhasma* as a light brown powder where tin tests as SnO[15].
Yashada (Zinc)	White, reddish yellow	Zinc oxide (ZnO)	White	(Zinc sulfide is yellow; zinc peroxide is yellowish-white; above 150ºC the latter decomposes releasing O_2). Mercury and/or sulfur are an accompaniment. The crystals of *bhasmas* (white) or off-white, brick-red/yellow (market samples) are hexagonal, just as in the mineral zincite (ZnO)[15,21]. In Hg and S are not an accompaniment[24].

conchiolin, glue like protein substance that is the organic basis of mollusc shells. By calcining the pearl finally calcium carbonate is obtained though in a very fine powdered state. The *prawala bhasmas* have shown very similar compositions (Table 3)[15,21,24]. The differences in the respective chemical compositions are only slight; a recent study revealed the CaCO3 content in *varatika bhasma* to be 98%[15]. But the methods of preparation differ and the *Ayurvedacharyas* treat these as different *bhasmas*[21]. Referring to the texts for the respective indications, one will find that these *bhasmas* address ailments that are largely common among them. Both Fe_2O_3 and $CaCO_3$ are polymorphic. The latter occurs in two crystal forms, aragonite (orthorhombic) and calcite (trigonal). *Manikya* (ruby) and *neelam* (sapphire) are chemically the same substance-aluminium oxide (Al_2O_3), with colour due to trace impurities of Cr, Fe and Ti. The crystal system of sapphire is hexagonal. That of ruby is a trigonal one which is considered a subdivision of the hexagonal crystal system. Their *bhasmas* are made following an identical method, in 8 iterations. The indications are quite similar but the *bhasmas* are regarded as distinct ones. The *abhraka bhasma* is made from mica, a complex hydrous potassium aluminium silicate. The preferred form is black mica, biotite, $K(Mg,Fe^{2+})_3(Al,Fe^{3+})Si_3O_{10}(OH,F)_2$. The calcination temperatures for mica lie in the range 700º-1,000ºC and 10 to 1,000 calcinations are prescribed. Mica is chemically inert and virtually unaffected by the action of heat, light, water, oils, solvents, alkalis and other chemicals. But the texts give very meticulous processes of its purification and emasculation. The end product has composition like that of mica only, powdered to the colloidal scales. It is brick red in colour, obviously due to the ferric oxide present therein. Various oxides present in the *abhraka bhasma* varying in proportions in a random fashion with the number of the calcinations mica was subjected to are listed (Table 4)[24,25].

Table 3—The *Prawala bhasmas*

Bhasma	Silicate	CaO	$CaCO_3$	$MgCO_3$	Al_2O_3
Mukta	x	x	95.5	x	0.92
Prawala	2.12	3.86	91.1	3.0	x
Shukti	0.45	x	95.2	0.49	x
Shankha	0.45	1.96	96.7	1.21	x
Varatika	x	0.97	99.5	0.04	x

The variations defy an explanation. The test report is not specific about which of the iron oxides was tested[24,25]. Going by the identification of the *bhasma* from its colour, the iron oxide as referred to is probably Fe_2O_3. Biotite shows up with FeO and Fe_2O_3 both whereas muscovite $KAl_2(Si_3Al)O_{10}(OH,F)_2$ in contrast has no iron oxides. FeO oxidizes to Fe_3O_4 and possibly to Fe_2O_3 also. Also, the report does not refer to potassium oxide which is pale yellow. The percentage of the various oxides is at a large variance, though the number of calcinations is not mentioned[5]. The only purpose large number of calcinations serve is for achieving fine scale particle sizes (Table 4). As for the medicinal properties, the *bhasma* has a wide range of indications to its credit. Largely, these resemble those of the *lauha bhasma*. Aluminium can be toxic, leading to many symptoms similar to Alzheimer's disease and osteoporosis, etc. MgO though is a medicinal substance. A *bhasma* that cannot be easily characterized is that of *vajra* (diamond), highly extolled as an aphrodisiac in the texts. The texts prescribe the *vajra* purification and emasculation with the urine of frog, donkey and horse; 14 calcinations are prescribed for its processing[24]. Diamond and graphite are two crystalline allotropes of carbon. The melting point of diamond is 4,027°C. It has extremely low chemical reactivity and is the hardest material known (hardness: 10 on Mohs scale). It tends to graphitize when heated to above 600°C in air. In oxygen itself, diamond begins to be oxidized at these temperatures. Carbon when strongly heated forms carbon dioxide only. When the air or oxygen supply is restricted, incomplete combustion to carbon monoxide (CO) occurs. Both the end products are gases only. The *vajra* has some other substances as accompaniment while its *bhasma* is being made. These include rock salt, or realgar (arsenic sulfide), cinnabar (mercuric

Table 4—The *Abhraka bhasmas*

Number of calcinations	Oxides of				
	Silica %	Alumi-num %	Iron %	Calcium %	Magne-sium %
50	50.7	12.6	18.8	4.34	9.45
100	27.5	12.1	32.0	3.82	1.84
500	26.6	31.2	12.1	7.15	0.57
1000	31.27	17.5	31.6	13.45	5.06
Colour	White/ clear	White	Red	White	White

sulfide) and pure sulfur, etc. Cinnabar sublimates at 584°C, while realgar also reacts with oxygen at high temperatures. The *vajra bhasma* is reddish in colour. By definition, a *bhasma* should show up as, or with an oxide of the metal/element incinerated. The oxidation process is not simple though and chemical analyses need to be done of the drug intermediates after each calcination and of the end product. These can confirm if the reddish end product is a mixture of sulfides and/or oxides of mercury and arsenic alone. White arsenic (*Malla* or *sankhia*) that is used in several ISM formulations is in fact arsenic oxide (As_2O_3), a white crystalline solid with a melting point of 315°C. When heated to 193°C, it sublimates giving a pure arsenic trioxide. When *malla bhasma* is made, eventually one gets a sublimated As_2O_3.

Bhasma as a medicine and the toxicity aspect

Minerals are essential for the proper function and structure of a cell. However, the human body cannot absorb most of the minerals in their natural (inorganic) form. The body has to recognize them as food. This food is provided by plants that process inorganic minerals from the soil into organic minerals that can be well absorbed by the human body. Concern has been expressed about the poisonous nature of the deified red sulfide of mercury (cinnabar/*makardhwaja*) and the red oxide of lead. There is a detailed description of their medicinal virtues in the texts[22]. Lead and mercury exposures of the human body and their harmful effects have been studied[26]. The absorption of inorganic compounds of mercury in the human body is poor to moderate when administered orally. Its half-life of stay in the blood is 40-60 days. The absorption of organic compounds of mercury is complete and the half-life in this case is about 70 days. Once absorbed, it is mainly distributed into the central nervous system and the kidneys. Its elimination is through excreta. Lead in both its inorganic and organic form is absorbed through the gastrointestinal tract. Once absorbed, it lands up in soft tissues (brain, liver, kidneys). Its half-life of stay in the blood is about 30 days. It is excreted through the kidneys. Chelation therapies have been used to bring down the levels of the toxic metals in patients. However, these require a careful monitoring. It has been expressed that probably the metals while being made into a *bhasma* get chelated with organic molecules (ligands) obtained from the herbs for these to be better assimilated[27]. To improve absorptivity and be less reactive in the digestive tract, a metal ion is bonded or chelated to an organic molecule, an amino acid or a hydrolyzed protein (a kind of a Trojan Horse). However, a *bhasma* when prepared is not a chelate; it tests to be an inorganic compound only. The *bhasmas* do show up with traces of certain other elements present in them. These come from the impurities, specific treatments and the crucibles and the vessels used[15,18]. Any organometallic complex compound has to survive the several incinerations at very high temperatures and if at all can be present in extremely small proportions only. Incidentally, minerals taken with a meal get usually automatically chelated in the stomach during digestion[28].

Thus, one has to contend with the simple inorganic compound form of the metal only that's medicinal value and the attributed pharmacological action is to be scientifically ascertained and its absorption and stay in the body is to be quantitatively determined till it is drained out. Many metal oxides are toxic; in comparison, a sulfide of a metal is generally less toxic compared to its oxide or chloride, being relatively less soluble in the body fluids. As *bhasmas* are mostly oxides only, the toxicities need to be evaluated. Probably, to check the toxic accumulations, a *bhasma* is traditionally administered with an *anupaana* (vehicle) such as honey, milk or butter, etc. This has been empirically known but the knowledge is mostly qualitative. Some of the observations as follows provide more definite indications to the safety factor behind the use of *bhasmas* compared to the plain salts of the same metals that are toxic in high doses. Recently, some detailed studies have been made of the physicochemical changes in the various stages while preparing *tamra* (Cu*) bhasma* by light microscopic, electron scan microscopic, X-ray diffraction and thermal gravimetric techniques using standard protocols[29]. Initially, copper sulfides and some new metallic complexes are synthesized but eventually it is free of copper. The particle size in the end product reaches colloidal levels. The study also found that the *bhasma* when given in higher doses to rats does not get absorbed in the gastrointestinal tract but gets excreted. A study on the neurotoxic effect and accumulation of methyl mercury and mercuric sulfide (HgS) in rats indicates that insoluble form of inorganic HgS can be absorbed from the G-I tract and that its neurotoxic potency is about one thousand times less than that of soluble MeHg[30]. In another study, *swarna* (Au) *bhasma* was prepared as per the

classical texts and was analyzed for its metal contents using atomic absorption spectrometry[31]. An infrared spectroscopy was performed that revealed it to be free of any organic compounds. Its acute oral administration showed no mortality nor did a chronic administration show any toxicity in experimental animals. Also, the *bhasma* was found to have antioxidant property.

Nanosubstances (0.1-100 nm) can have special physical and chemical properties. These are comparable to the size range of biological structures and so are potential substance for manipulation, sensing and detection of biological systems. A single atom is 0.1 to 0.2 nm in size, a strand of DNA is 2 nm wide while a red blood cell is about 7,000 nm. Substances such as metal oxide nanoparticles, nanogold particles and carbon based nanomaterials (fullerenes, nanotubes, nanodiamonds), etc. are being viewed as nanomedicine, with a variety of biological applications, in the diagnosis and treatment of a wide variety of diseases. At these scales, many substances can develop toxicity too. Experiments with zinc oxide nanoparticles (nZnO) have shown selective toxicity to different bacterial systems and human T lymphocytes[32]. Gold and its compounds have been known for their therapeutic utility. A standardized colloidal gold preparation (Tyndall's purple, Au°, 27 nm) has been found to be a far more effective anti-arthritic agent in rats than the sodium aurothiomalate used in the treatment of rheumatoid arthritis[33]. The administration route was subcutaneous; attempt was to examine if the classic *swarna bhasma* can also be similarly suitable. *Swarna bhasma* (42 iterations, 900 C) was prepared brown red in colour following classic texts (*Rasaratnasamuchchya and Sarangdhara-Samhita*). An infrared spectrum showed no presence of organic compounds and transmission electron microscope (TEM) measurements revealed average particle size to be 57 nm with globular morphology. An atomic absorption spectroscopy indicated the *bhasma* to be free of any mercury but having 92% zerovalent gold (Au°) in the *bhasma.* These nanogold particles should be able to reach the affected site even if administered orally and provide a slow and sustained release of Au (I) ions[33]. By itself, this is a highly promising area for further studies on treatment of diseases.

However, an altogether different form of a *bhasma*, obtained following a classical *bhasma* process has been used. The *swarna bhasma* process is a temperature sensitive one and one must settle it if the *swarna bhasma* so obtained - predominantly a colloidal metallic gold - is a drug intermediate only since the *bhasma* process in general is so designed as to produce an oxide, free of organic and metallic particles. The classic texts describe a method involving aqua regia etc. to produce pure and fine yellow coloured gold powder which is used as medicine, in place of gold foils but it does not involve incineration[4,24]. As an aside, note that colour of a colloid can differ depending on particle size, shape and mutual separation, and refractive index of the medium. Nanogold particles 2-30 nm in size in a colloidal suspension are bright red in colour and their colour changes to purple and blue as the size gets larger as a result of a phenomenon called surface plasmon resonance[34]. Nanodiamonds are being considered as a potential drug delivery agent that can carry drugs to certain parts of a damaged cell where larger carbon based nanoparticles cannot reach and interestingly the left-over nanodiamonds do not induce inflammation in cells. Their impact on humans and other biological systems is being studied. It has been demonstrated that 2-10 nm nanodiamonds are biocompatible with a variety of cells of different origin and are nontoxic[35]. Nanodiamonds can for example be produced in a detonation of TNT/RDX at 5 Gigapascals and 2,000°C. The nanodiamond concept differs altogether from that of a *vajra bhasma* and so a correspondence can not be made. The *bhasma* process does not create nanodiamonds as an end product since powdered diamond will be only oxidized away in the numerous incinerations. Nanomedicine is regenerative medicine, for the treatment or repair of tissues and organs, within the targeted cells. The classic *bhasma* could qualify to be in the new age nanomedicines realm but the correspondence should be done within propriety. Cheap surely but whether therapeutically suitable is another matter that requires detailed studies, particularly of the toxicities.

The Indian medicines were subjected to critical examination using the standards applied to western medicine where permissible limits to the presence of a toxic heavy metal in a formulation are established[1]. The work is about metal-contents and not a study of metal toxicities among populations resulting from use of such medicines. Also, the metals chemical forms, which can impact bioavailability and toxicity could not be ascertained. This important aspect has not

received the attention it deserves. As inorganic compounds and in prescribed dosages, they are less likely to accumulate in the body. With particle sizes in the micron to near nanoscale range, the absorptivity of the metal *bhasmas* is presumably better than an ordinary mineral taken in powdered form. Between them, these factors are contrapositive but can also strike a kind of a balance. If the preparations have been done as expounded in the texts, the toxicity aspect is constrained because the compounds have been traditionally in use. All of the *bhasma* metals are not toxic. The Ayurvedic Formulary of India as also the National Formulary of Unani Medicine list several formulations that contain *malla* (arsenic) as an active pharmaceutical ingredient. The upper limit to the per diem dosage is 10 mg, for an adult. The formularies do permit usage of As. In very small doses, it is stomachic, general and nervine tonic, alterative, respiratory and sexual stimulant as per the texts[22]. There are several metal compounds considered poisonous but are permitted to be used in an ISM formulation. There are numerous *vaidyas* and ISM drug manufacturers who have developed formulations from less controversial drug material, permitted to be used in ISM, and claim positive results. These need a multifaceted study, like any modern medicine today.

The concerns in the study notwithstanding, use of inorganic chemical substances in medicine has been widespread in the West, well into the 20th century and these have been part of pharmacopoeias[1]. One can cite here substances such as compounds of mercury, copper sulfate, alum, magnesia, borax and green vitriol, etc. The West has used arsenic trioxide over the past 200 yrs as a part of medicine, including the treatment of cancer. The Food and Drug Administration in 2000 approved arsenic trioxide for the treatment of patients with acute promyelocytic leukemia that is resistant to ATRA. One can see a number of tonics in US, UK, etc. which contain a number of minerals including vanadium, manganese, chromium, selenium, etc.

Standardization and quality control

The Ayurvedic Formulary of India lists more than one method of preparation of the *bhasmas* of some metals while the Drugs and Cosmetics Act lists several traditional texts that a *vaidya* can refer to for preparation of a bhasma[19]. A standardization of process and the end product both is called for (Table 2). Pharmacopoeial standards have been published by the Government of India for a large number of single drugs of plant origin and the work on classical composite formulations is being carried out in several Indian laboratories. The CCRAS has developed a technique called phased spot test for identification and quality assessment of *bhasmas*[9]. In recent years, sophisticated test equipments and techniques of data analysis have been put to fruitful use for the physicochemical characterization of the bhasmas[14-17,29]. These studies also explored intensively the different *bhasma* preparation methods of the same metal, chemical nature and crystalline structure of the intermediates and the final products. These have involved Atomic Absorption Spectrophotometry (AAS), flame photometry, Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES), X-ray diffraction (XRD) analysis and *p*Hmetry, etc. The AAS uses the property of atoms to absorb certain wavelengths of electromagnetic radiation. The amount of light absorbed enables one a quantitative estimate of the absorbing element. The ICP-AES uses a plasma (e.g. inductively coupled plasma) to generate excited atoms. These atoms emit electromagnetic radiation at a wavelength that is characteristic of a particular element. From a measure of the intensity of this emission one can quantify the concentration of the element present in a sample. The techniques involving X-ray diffraction analysis reveal information about the crystallographic structure (arrangement of molecules in a crystal) to know whether the particles are crystalline or amorphous and the chemical composition and physical properties of materials. From results on particle size distribution and crystal structure, one can determine how well the *bhasma* process has proceeded. With such equipment in hand, it should be possible to standardize and freeze the SOPs for *bhasma* preparations. A ten point's protocol has been suggested for standardization of *bhasmas* and the process of their preparation[29]. One of these is the need to distinguish the *bhasma* of some heavy metals from those of the toxic ones.

A standardization programme should also distinguish between *bhasmas* of metals made with herbs and non-toxic minerals, and those with toxic substances. There is a need for precise quantitative information on the oxidation kinetics, oxide growth and the chemical composition changes specific to each metal, metal mixtures and alloys, and, calcination cycle while one prepares to make a

bhasma. These should be batch size specific as oxidation rates may be different if batch sizes and the hearths differ. This will have a direct impact on the composition of the *bhasma*. In each cycle, the oxidation process progresses in a complex way. The oxidation rates are determined by various physical processes (gas adsorption, solid state diffusion, etc.). These are also affected by factors like kiln temperature, particle size, surface characteristics and oxide scales, reaction time and the gas composition. The oxidation rate of a large number of metals at temperatures below 400˚C is known to follow logarithmic time dependence. At high temperatures the oxidation of many metals follows parabolic time dependence, where the rate of reaction is inversely proportional to the square root of time. In both, the reaction rates decrease with time. In contrast, the reactions may follow a linear law where the rate is constant with time. However, the oxidation reactions are not simple and under certain conditions, these are observed to follow a combination of the rate laws, suggesting that the process is a nonlinear one[36]. This simply means that oxidation follows simultaneous mechanisms one of which predominates in the initial phase while the other dominates after extended oxidation. As the calcination process is initiated, a certain time shall elapse before the oxidation reaction can be taken to have begun. For traditional hearths of different capacity and for each cycle, temporal profiles of temperature, T ($t-t_0$) where t_0 is the time from when one assumes the reaction begins can be constructed. The parameter t_0 is not easy to ascertain. A number of trials shall be needed; one could also take it as the time when the heating is begun. This will be useful in tracking the progress of the process where, after each cycle, one should also determine the amount of metal used up and the amounts of oxide produced, and construct oxide growth rates. These findings can be used to calibrate a new technology kiln.

In the low and high temperature regimes respectively, some metals form different oxides. For example, iron when heated in air above 150°C forms Fe_3O_4 (black) but as the reaction proceeds, Fe_2O_3 dominates; the latter when heated above 1,200°C in air gives Fe_3O_4 and O_2[37]. The presence of other chemical substances also modifies the oxidation process of a metal. For instance, elements heated with sulfur form sulfides; metallic sulfides when heated in air get converted into the oxide of the metal and sulfur dioxide[20]. The oxidation process is more complex in the case of metal mixtures and alloys. The metals may play dopants and it is possible that mixed metal oxides too are formed. When the respective melting points are different, the constituent metals get selectively oxidized affecting temperature profile and reaction kinetics. It will be useful to know how the proportions of oxides vary in comparison to the relative proportions of the metals in the parent substance during and with each cycle. Brass and bronze do not have their constituents alloyed in a unique proportion. Here, Sn and Zn will begin to oxidize earlier than Cu due to their melting points being much lower than brass (900°-940°C depending on Zn proportion) and bronze (950°C) and affect the ongoing oxidation process. For instance, in the case of brass directly heated in air at 500°C for two days, the XRD spectra revealed, apart from the Cu-Zn alloy peaks, those due to Cu_2O and CuO nanostructures when the Zn content was below 10%; ZnO showed up with Cu_2O and CuO phases when the Zn content was between 10%-30%; CuO was but Cu_2O was not present when the Zn content was about 30%, whereas only ZnO phase was present when the Zn content was about 40%[38]. As for Cu_2O, it is stable in normal conditions but will gradually oxidize to CuO in moist air. This is just to illustrate the way oxidation reactions can proceed and how x-ray diffraction studies at each stage can provide valuable information on the phases present.

In the name of a wider reach, the *bhasma* making is on its way from the backyards of the *vaidya* to a manufactory, where the end products will be made in batch sizes of unprecedented kind. Strict adherence to the processes as delineated in the classical texts ensured that the finished product was as expounded but in the absence of a personal and qualified touch the classical operating procedures may get compromised. In addition, one has to contend with factors such as seasonal availability of certain crucial herbs, questionable quality and storage of drug material of animal origin, etc. To ensure the desired quality, production of *bhasmas* needs to be carefully monitored, with in-process laboratory tests and documentation. The GMP norms will bring about a paradigm shift in the concept of processing. The first major change in the *bhasma* process is the dispensing with the first step, namely the prescribed cleansing of the parent drug material. Often these shall come cleaned up or purified right from the supplier,

supported by laboratory tests. The more crucial change however relates to the hearths and the crucibles/earthen pots traditionally used which are critical heat and air supply managers. The oxidation kinetics will have to be reworked for new technology kilns/ovens. The last but an important step of the standardization programme will lay in the clarity and exactness in the label claims. The main API and the traces present can find mention on the label along with the references to the standard texts while other analytical information could be relegated to the insert literature.

Discussion and conclusion

The *bhasmas* have all along been a mystery, as substance and as medicine. While the naturally occurring metal carbonates, sulfates and silicates also have been used in medicine, the *bhasmas* have held a tremendous sway on the *rasavadins* (alchemists) and the practitioners for centuries. These reflect great depths of the alchemical expertise of the times, where one can see a great deal of experimentation in the eventual identification of choice elements and substances as potential medicines and development of processes around them. While they were killing a metal to harness its latent powers and make wonder substances, the *rasavadins* did not know what exactly they were arriving at or handling-simple inorganic compounds. This was also their tryst with a technique which today we refer to as nanotechnology. The most remarkable thing about the *bhasmas* of some metals and gems is their incorporation into the Indian Medicinal Systems as drugs and their having stayed so over the ages firmly. The practitioners gained in empirical wisdom and with time, the safety aspect of the *bhasmas* was perfected even though most of the empirical evidence has been only qualitative. Where does one draw the fine dividing line between a medicine and a toxic substance? At a fundamental level, the *bhasma* as a medicine needs a detailed scientific scrutiny. It may defy the modern definition of a medicine but the body of available clinical data can lead the researchers to examine their function as a medicine and settle the crucial question of accumulation of heavy metals by the human body, the associated toxicities and the ways to flush them out.

There is no standard *bhasma* of a metal as such. Different compounds of a metal resulting from different methods of preparation passing off as the same *bhasma* and addressing the same ailments were also found. Also, the end product may sometimes be unstable. All this has to be resolved so that there is one specific process to a metal and the resulting *bhasma* is a duly identified substance. The possibility of different *bhasmas* of a given metal provides also an opportunity to enlarge the scope of a standardization programme. By subjecting these variants to extensive clinical tests the common indications as documented can be resolved into the compound-specific ones. Experiments in crystal engineering with the *bhasmas* to produce the desired polymorph form can open up a rich field of research in the traditional Indian medicine. A common ground to thought and practice also is needed in the manufacture and administration of *bhasmas* as medicines. The practitioner needs to be explained to and provided with clear information on a manufactured medicinal product, the laboratory and clinical test results, proper dosages, presence of other elements and compounds and their pharmacological implications, toxicity studies, clinical management of exposure of toxic substances beyond the levels seen in the general population and drug interactions, etc. An imprudent administration of the *bhasmas* as single or compound drugs can lead to serious consequences. There have been instances when the diagnosis was correct but the drug itself was not agreeable to the constitution of the patient[39].

A broad discussion on safety issues in the Indian Systems Medicines has been presented[40]. In the case of proprietary metal formulations, the onus to follow all this up is on the manufacturer, who should carry out estimations for adverse drug reactions and toxicological studies to establish lethal dosages. These should be prescription drugs with clear label claims, to be taken under medical supervision while the insert literature could contain relevant technical information on the product as also caution the user against exceeding the stated dosages. It will be most appropriate if the ISM speaks and is taught in modern scientific language adopting scientific methodology, modern instrumentation and analytical techniques so that a multidisciplinary communication can fructify[17,41]. Further, new established knowledge should receive prominent place in the curricula, to be reviewed every 5 yrs or so. The regulatory machinery interacting with manufacturers needs to be periodically refreshed on new developments. There is a great awareness among the public, keen to try it out. But, instances of doubtful processes, adverse drug reactions and aggressively advertised suspect

formulations also have come to light. These need to be checked as these can cause undue distrust in the traditional knowledge.

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