Review Article

Bioavailability Enhancement of Partially Water Soluble Solid Medicament in Traditional System of Medicine

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Liquid state medicaments like *Kwatha* (decoction), *sneha kalpa* (oleaginous preparation), *asavarista* (biomedical fermentation) are supposed to have higher bioavailability due to higher absorption whereas solid state medicaments such as herbal *churna* (powder), *bhasma* and herbomineral formulations has theoretical low bioavailability, this may be due to poor water solubility. It has been claimed that *bhasma* is very effective at low dose. A question about how *Bhasma* and other preparations be effective in very low doses despite lower water solubility needs to be answered. In a bid to find the answer ancient and contemporary literature was scrutinized with respect to pharmaceutical aspects. It was found that particle reduction technology improved solubility, and bioavailability and particle size reduction technologies such as *bhavan*, and *bhasmikaran*. Were practiced in Ayurveda, which might correspond to liquid assisted grinding and tribochemistry. Particle size below 1 mm causes disruption of solute-solute interaction and increases bioavailability. Tribochemistry may produce nanoparticles either mechanically or by thermally-induced chemistry at the asperity tips due to flash temperatures and one affects the other. The reaction of solid state components during liquid-assisted grinding also is an important method responsible for the conversion of inert precursors, such as metal oxides, into hybrid inorganic-organic materials. Thus particle reduction technology enhances the bioavailability of poor water soluble components, apart from that use, liquid media in process supposed to assist the particle reduction technology and potentiation. Thus, with the help of suitable particle size reduction technology and synergistic action bioavailability of poorly water soluble components could be enhanced.

Key words: Tribochemistry, mechanochemistry, *bhavana, bhasmikaran*, bioavailability, nanotechnology

Therapeutic efficacy of medicaments is dependent on its plasma concentration, which in turn depends on the bioavailability. It is an important pharmacokinetic property of therapeutic agent, which is defined as a fraction of the administered dose of unchanged drug that reaches the systemic circulation[1]. It depends on numerous factors such as aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and among them aqueous solubility is the most critical parameter influencing the ability of a drug to be available in suitable concentration at the site of action regardless of the pharmaceutical dosage form and route of administration[2,3]. This indicated that poor solubility of a drug might limit the clinical efficacy by diminishing the bioavailability[4]. Thus reduced aqueous solubility is one of the key hindrances encountered during new drug or drug product development.

Herbs, metals, minerals and animals are chief source of *materia medica* of Ayurvedic system of medicine and before using as therapeutic agent, these are converted in to suitable dosages by applying pharmaceutical principles[5]. It is well known that maximum number of dosage forms of Ayurvedic system are either solid state (*churna*-powder, *bhasma*-ash *vati*-tablets), or liquid state (*swarasa*-expressed juices, *kwatha*-decoction, *sneha kalpa*-lipid base formulations). Among the solid dosage form, *churna*, *bhasma* and *vati* are less water soluble, but have been the main stay of various therapeutic regimen in Ayurvedic system of medicine. Coincidentally, among the approved and currently used drugs as well as those in developmental pipeline, 40 to 70% of drugs were water insoluble as reported

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in contemporary literature[6-8]. Lower solubility in the gastrointestinal fluids limit bioavailability. This induced us to ponder how our ancient scholars successfully treated various diseases with herbs, metals and minerals although many of those were known to be water insoluble.

Thus we assumed that pharmaceutical technology involved in the preparation of dosage forms might have ensured that the active principle of the Ayurvedic preparations have adequate aqueous solubility in *kwatha*, *hima*, *phant*, or lipid soluble in *sneha kalpa* through amalgamation of one or more processes depending upon nature of medicament. The objective of this review is to explore the traditional technology used to explore the bioavailability of poorly water soluble active components with contemporary scientific knowledge and understanding.

References of solid medicament and their principle of preparation have been taken basic manuscripts of Ayurveda, Rasa classics and other Ayurvedic treatises, Pharmacopoeias (Ayurvedic Formulary of India, Ayurvedic Pharmacopoeia of India), indicated in schedule I of Drugs and Cosmetic Act 1940. A search was undertaken in Google Scholar, ScienceDirect, PubMed database and other relevant databases, using keywords like particle reduction, grinding etc. and relevant terminology that may be helpful in understanding of bioavailability of poorly water soluble drugs in light of science.

Observations:

Solid state medicaments such as herbomineral formulations are frequently used in Ayurvedic system of medicine since its inception for treating several ailments and these were mainly prepared by process of *bhavana* using selective liquid media (Table 1). Furthermore, *bhavana* process, which was equivalent to liquid-assisted grinding might actively participate in different processes like *shodhan* and *bhasmikaran*, responsible for preparation of efficacious solid medicaments (Tables 2 and 3).

It has been established that solubility of a substance could be increased by increasing the dissolution rate, which may be accomplished either by particle size reduction or modifying crystal habit[9]. It is well established that particle size is an important factor accountable for solubility and bioavailability of drugs[10]. It is also reported that particle size below 1 mm causes disruption of solute-solute interaction, increases solvation pressure and affects the kinetic solubility, which eases the dissolution, thus significantly increasing solubility[11,12]. Furthermore, solubility increases by increasing the surface area available for solvation[13,14]. Thus, particle size reduction technology is a safe method to increase solubility of substances without altering the chemical nature of the drug[10] and can routinely be used to increase the bioavailability of poorly soluble drugs[14]. Before using as a therapeutic agent, solid medicaments of Ayurveda are converted in to a powder (*churna*) by the process of grinding. Mechanical energy originated due to the grinding process is responsible for breaking the order of the structure, producing cracks to generate new surfaces and at the point of impact of the edges the solids deform, forming hot points where the molecules can reach very high vibrational excitation leading to bond breaking and ultimately small particles are generated[15]. Coarse powders are subjected to further process by another principle (decoction etc.) before using in a specific disease whereas fine powder is directly used for therapeutic purposes indicating that coarse powder is not therapeutically effective in normal dose. The particle reduction technologies are not only simpler, economical but also ecological friendly. The activation of chemical reactions by mechanical energy can lead to many thought-provoking applications, ranging from waste processing to the production of advanced materials with novel microstructures. Therefore this technology is used for the poorly water soluble medicaments derived from herbs but, in case of metals and minerals, this technology cannot be directly fruitful. Another methodology can be used to resolve this issue.

***Bhasmikaran*:**

Bhasma an Ayurvedic metallic/mineral preparation (Table 1) prepared by *Bhasmikaran* process. It is a process by which bio incompatible substances converted in to biocompatible by certain *samskar* and/or other processes[16]. In includes cyclic involvement of two main process *Bhavana* (liquid assisted grinding) and *puta* (energy required for conversion of metals and minerals in to therapeutically administrable forms). In *puta* system, purified material is subjected to grinding in presence of small quantity of specified liquid and after completion of process it is subjected to ignition at high temperature, these process is a likeness to tribochemistry in contemporary science, which is the coupling of mechanical and chemical phenomena on atomic and molecular scale that include mechanical breakage, chemical behaviour of mechanically-stressed solids[17]. The chemistry that occurs between

TABLE 1: *BHAVANA* IN PREPARATION OF HERBOMINERAL FORMULATIONS

Manuscripts	*Bhavana Dravya*	Formulation	Reference
Bhaishjya Ratnavali	*Arka patra Swarasa*	*Icchabhedi Rasa*	BR
	Triphala Kwatha	*Hridyarnava Rasa*	BR
	Hastishundi Swarasa	*Kalyana Sundar Rasa*	BR
	Ardraka Swarasa	*Hingula Shodhana*	BR
	Guduchi Swarasa	*Dhatri Loha*	BR
	Arjun Twaka Kwatha	*Nagarjunabhra Rasa*	BR
	Ksharodaka	*Taladi Ksharanjana*	BR
	Gomutra, Bhringaraja Kwatha	*Sudhanidhi*	BR
	Bhringaraja Swarasa, Sharpunkha Swarasa	*Shitapittabhanjana Rasa*	BR
	Ardraka Swarasa	*Mahodadhi Vati-2*	BR
	Kushamanda Swarasa etc.	*Talkeshwara Rasa*	BR
	Guduchi Swarasa etc.	*Grahnivajrakapat Rasa*	BR
	Brahmi Kwatha etc.	*Garbhachintamani Rasa*	BR
	Guduchi Swarasa etc.	*Amvateshwara Rasa*	BR
	Ardraka Swarasa etc.	*Ajirnabalakalanala Rasa*	BR
	Sarpa Visha etc.	*Trailokyachintamani Rasa*	BR
	Chitraka Mula Kwatha	*Virbhadrabhraka Rasa*	BR
	Chitraka Kwatha	*Agnikumara Rasa*	BR
	Ikshu Swarasa etc.	*Muktapanchamrita Rasa*	BR
	Bhringaraja Swarasa	*Rajrajeshwara Rasa*	BR
	Chitraka Kwatha	*Agnikumara Rasa*	BR
	Nimbapatra Swarasa	*Manikya Rasa*	BR
	Ardraka Swarasa	*Jwaradhumketu Rasa*	BR
	Bhringaraja Swarasa	*Shilagandhaka Vatika*	BR
	Shatavari Swarasa	*Bhaskaramritabharaka*	BR
	Kushmanda Swarasa, Kanji	*Talkeshwara Rasa*	BR
	Chitrakamula Kwatha	*Meghanada Rasa*	BR
	Ardraka Swarasa	*Mahodadhi Vati-2*	BR
	Kushamanda Swarasa etc.	*Talkeshwara Rasa*	BR
	Guduchi Swarasa etc.	*Grahnivajrakapat Rasa*	BR
	Chitrakamula Kwatha	*Tridoshniharvinashsurya Rasa*	BR
	Ardraka Swarasa	*Kaphaketu Rasa*	BR
	Kakmachi Swarasa, Shatavari Swarasa,	*Indu Vati*	BR
	Triphala Kwatha	*Ardhanarinateshwara Rasa*	RSS
	Ardraka Swarasa	*Ahiphena Shodhana*	RT
Others	*Amalaki Swarasa*	*Amalaki Rasayana*	CHK
	Kantakari Phala Swarasa	*Ajirnakantaka Rasa*	SSMK
	Nimbapatra Swarasa	*Arogyavardhini Vati*	AFI

BR: *Bhaishjya Ratnavali*, RSS: *Rasa Ratna Samucchya*, RT: *Rasa Tarangini*, CHK: *Charak Samhita Kalpa Sthan*, SSMK: *Sharangdhar Samhita Madhyam Khand*, AFI: Ayurvedic Formulary of India

TABLE 2: *BHAVANA* IN PREPARATION OF *BHASMA*

Bhavana Dravya	*Bhasma*	References
Jambiri juice	*Kasisa*	RT
Triphala Kwatha	*Lauha*	RRS
Vata	*Abhraka*	RRS
Arka	*Hartala*	RT
Eranda	*Swarna makshika*	RRS
Dhattur	*Parada*	PS
Gulab Arka	*Mukta*	RT
Pudina Arka	*Hingula*	*Bhasma Vigyaniya*
Kevda Arka	*Akika*	*Bhasma Vigyaniya*

RSS: *Rasa Ratna Samucchya*, RT: *Rasa Tarangini*, PS: *Parad Samhita*

TABLE 3: ROLE OF *BHAVANA* IN DIFFERENT PHARMACEUTICAL PROCESSES

Process	*Bhavana Dravya*	Name of drug	Reference
	Agastya patra juice	*Manahshila*	RRS
Shodhan	*Ardraka* juice, Latex of *Ahiphena*	*Hingula*,	RRS, BR
	Bhringraja juice (soaking)	*Kasisa*	RRS
	Palasha mula twaka Kwatha	*Hartala*	RRS
	Gavjabana Arka	*Sangeyashab*	RT
Bhasmikaran	*Go Kshira*	*Mukta*	RT
	Aja Kshira	*Hartala*	*Bhasma Vigyaniya*
	Aja Kshira	*Hartala*	*Bhasma Vigyaniya*
Amritikarana	*Panchamrita, Kumari* juice	*Tamra*	RT
Lohitikaran	*Rakta varga dravya*	*Abhraka*	RT
	Arka Kshira, Tila Taila	*Hartala*	RRS
Satvapatan	*Ghrita*	*Manahshila*	RT
	Karanja Taila	*Tuttha*	RT
	Mushli Swarasa	*Abhraka*	RRS

RSS: *Rasa Ratna Samucchya*, RT: *Rasa Tarangini*

the lubricant and environment with the rubbing surfaces under boundary lubrication conditions is known as tribochemistry[18]. It includes specific reactions that occur only during rubbing and chemical interactions (oxidation, thermal degradation, catalysis, and polymerization) with the surface. In this process, two sets of reactions are intimately intertwined and one affects the other.

There are two possible sources of tribochemistry: the mechanically induced chemistry (fresh nascent surface, electron emission) and the thermally induced chemistry at the asperity tips due to flash temperatures[19]. In mechanically-induced chemistry, energy required to activate chemical reactions and structural changes comes from mechanical process. Thus by these steps metals and mineral used in Ayurvedic system is converted to *bhasma,* which is supported by contemporary finding such as ultrafine grinding of minerals, such as chalcopyrite or sphalerite (*Makshik*), is known to increase chemical reactivity so that the valuable constituents can be leached under far less severe conditions than would normally be required[20].

***Bhavana*:**

The pharmaceutical process in which metallic and mineral as well as herbal powders are subjected to *mardan* (grinding) with liquid media (*swarasa*, *kwatha* etc.) till complete absorption of liquid by the powder is known as *bhavana*[21]. Grinding, the central manufacturing process involved in particle size reduction, production of large surface area and also responsible for liberation of valuable chemical from their matrices. It is energy consuming process, which may be expended for lattice rearrangements and mechanochemical reactions (reshuffling of interlaced structure) depending upon the nature of materials[22]. Furthermore, energy can be consumed between friction of the particles and the grinding media as well as between particle and particle. It is reported that the actual energy needed for fracture required to produce new surface area is only a small fraction (<1%) of the total energy input of grinding mill and greater proportion of the energy input (>75%) is lost in the form of heat, which would increase temperature that might lead to loss of therapeutic efficacy of thermolabile substances[22]. By adding a small quantity of a liquid to prevent increase in temperature thus might account for the facilitation of the chemical process.

Grinding operation mainly involves two major processes namely pulp flow and stress application in simultaneous manner and these processes include transport of material to the grinding zone and subjecting to the grinding actions, leading to possible propagation and initiation of cracks. Breakage of a particle can be achieved if the particle is captured in the grinding zone and subjected to a fruitful breaking action. The probability of breakage is the product of probabilities for the above two basic processes[23]. Eqn., $P=P_c \times P_b$, where P is the overall breakage, P_c is the capture of breakage and P_b represents the breakage upon capture. The probability of P_c is defined as the probability of a particle that will be captured in a grinding zone and P_b is interrelated to the particle strength.

Pulp flow process:

Pulp flow process (transport of material inside a mill) largely depends on the pulp fluidity that is influenced by the state of aggregation or dispersion of particles

inside the mill and further determined by the nature of interactions between the particles and the grinding media. Modification of the pulp fluidity has been considered a special potential for increasing the efficiency of the grinding process because it determine how well particles are transported to regions where grinding action is most severe[23]. In the *bhavana* process, addition of small quantity of liquid may change the pulp fluidity, which helps in particle size reduction.

Stress application process:

Size reduction of solids is achieved by subjecting particles to different stresses that involve rupturing of chemical bonds to create new surfaces and retard re-joining of the ruptured surfaces[24]. In process of *Bhavana*, breaking of solid particle subjecting to particle stresses in grinding zone is responsible for initiation and propagation of several cracks that leads to numerous fractures in each particle. These fractures may occur within the particle itself (intra granular fracture) or along the grain boundaries (inter granular fracture). Intra granular fracture is sufficient for size reduction whereas inter granular fracture is required for liberation. It has been well established that all natural materials have defects in the form of cracks, flaws or dislocations and these defects will act as stress modifiers leading to decreasing the strength of particle. It has been supposed that liquids such as water played an active part *bhavana* process and adding surface active agents could be amplified the process[25,26].

Effect of the environment on grinding:

From the Table 1, it is obvious that formulation prepared by grinding with presence of liquid is mentioned for the treatment of several disorders. Furthermore, as mentioned in basic manuscripts of Ayurveda that by grinding of *drayva* with liquid media of its similar properties potentiate the efficacy of that *dravya* powder[27]. Previously, grinding has been considered as a physical process controlled only by the mechanical conditions and wet grinding (grinding with liquid) is more efficient than dry grinding[28]. Published literature showed that presence of small amounts of appropriate solvents have made a significant improvement in the rate of product formation[29] and grinding with organic liquids was found more efficient than with water[30,31]. This infers that formulation prepared by grinding with liquid would be more effective than grinding without liquid, this could be the reason that Ayurvedic scholars prepared the medicament by grinding with liquid and were able to reduce particle size with potentiation of the medicament.

Nanotechnology and *bhavana*:

Nano sizing, a particle size reduction technique employed to enhance the bioavailability of poorly soluble drugs[32] and nanoparticles are considered as promising new medical tools, leading to the formation of a protein corona that mediates interactions with biological environment[33]. These particle are divided into two groups such as organic (liposomes, micelles) and inorganic (gold, silica, iron oxide) and can be used for therapeutic as well as diagnostic purposes[34-38].

***Bhasma* as inorganic nanoparticle:**

Bhasma, are unique dosage form mentioned in Ayurvedic system of medicine may be considered as nanomedicine and is free from toxicity in therapeutic doses[39,40]. This invites for intellectual analysis technology involved in creation of *bhasma* in ancient time. It is observed that *bhasma* are prepared by particle reduction technology (grinding with presence of small quantity of liquid) followed by high temperature synthesis[41]. The conventional particle size reduction still remains a basic size reduction procedure but particle size reduction techniques such as nanotechnology and nanosization i.e. nanosize particles (<100 nm in diameter), currently increasing attention of researcher[42] and widely studied for the formulation approaches to drugs with poor aqueous solubility. Particle size reduction to nanosize range involves two processes namely 'bottom-up' and 'top-down techniques'. The bottom-up technologies start from the molecules, which are dissolved and then precipitated by adding a solvent to a non-solvent and top down technologies are disintegration methods involving wet milling and provide more efficient size reduction than the conventional size reduction techniques[43] and mainly used in synthesis of molecule in western system of medicine and Indian system of medicine, respectively. It has been reported that in mechanochemical reaction, temperature initially increasing slowly with time. After some time, increase temperature abruptly suggesting ignition, to avoid combustion reaction controlling the milling condition like addition of diluents, reducing reaction rate etc. and appropriate selection of milling reduce the reaction rate[44], thus reaction may proceed in steady state manner[45] that may cause formation of desired product. This indicates that *bhavana* process involved in process

of *puta* may also incorporate further processes and helpful in production of nanoparticles in *bhasma*.

Sneha kalpa as organic nanoparticles:

Liposomes are nanoparticle has great potential for improving the therapeutic efficacy and come under group of the colloidal carriers because of their better stability and ease of commercialization[46,47]. As per the liposomal theory, liposome is prepared by homogenization, shaking and heating method and oleaginous in nature. In its manufacturing process interaction between lipid-lipid or lipid water may occur and finally active ingredients are in both aqueous and lipid media[48-50]. From Ayurvedic literature it is clear that *Sneha kalpa* is an oleaginous medicaments prepared from the substances like *Kalka* (herbal paste), *Kwatha* (decoction) or *Drava Dravya* (liquid media) by unique heating pattern[51]. It has been well known that distribution of drugs is chiefly influenced by its lipid solubility and lipid soluble drugs are readily diffuse in cerebrospinal fluid because of permeability to blood brain barrier, which is lipophilic in nature[52]. Thus we assume that *sneha kalpa* has great similarities of liposomal that may enhance to bioavailability of low water soluble medicament especially to central nervous system.

Bhavana and herbomineral formulations:

Herbomineral formulation is the most promising form of treating diseases from acute (fever) to the chronic (cancer) due to faster relief, fewer and convenient doses which are efficacious as compared to only herbal drugs. Constituents of herbomineral constituents such as gold, silver, lead, iron and arsenic have never been used in the raw form due to toxicity[53,54], yet found very efficacious after *shodhan* (purification and potentiation) performed as per Ayurveda principles. These herbomineral formulations are mainly prepared by grinding/*bhavana* process, which could be responsible for the conversion of inert precursors, such as metal oxides, into hybrid inorganic-organic materials[55]. It is a fast and effective way to obtain new solid state forms, which could not be obtained by solution methods for reasons of solubility or immiscibility of reactants[56]. It is significantly broadened by techniques such as liquid assisted grinding[57], which make it possible to access different polymorphs and also promote reactions that were unsuccessful under neat grinding[58,59]. Thus by *bhavana* process, inert precursors such as metal oxides are converted to herbomineral formulations, which could be effectively used in therapeutics.

Bioavailability of fewer water soluble solid medicaments has been enhanced effectively in ancient as well as contemporary science by applying the principle of particle reduction technology. Particle reduction technology of ancient science like *bhavana*, *bhasmikaran*, and *churnikaran* might correspond to liquid assisted grinding, tribochemistry and mechanochemistry, respectively. Besides particle size reductions by ancient technology bioavailability could also be enhanced.

Conflict of interest:

The authors report no declarations of interest.

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