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MODERNIZATION OF AYURVEDIC LIPID FORMULATIONS THROUGH ADVANCED NANOTECHNOLOGY: BRIDGING TRADITIONAL WISDOM AND CONTEMPORARY DRUG DELIVERY

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ABSTRACT

The Ayurvedic lipid formulations like ghrita and taila made by Sneha Kalpana method are one of the most ancient lipid-based drug delivery systems among the history of pharmacy which is still beyond the scope of mainstream literature of nanotechnology or formulation science. The scientific basis for classical Sneha Kalpana preparations is briefly reviewed and more contemporary approaches to lipid-based drug delivery systems are discussed and described and are shown to converge mechanistically with the classical Sneha Kalpana formulations using the Lipid Formulation Classification System of Pouton. Polar active botanical ingredients of classical ghrita have been found to be present in micro and nano-vesicular formulation (nanosolar capsule) in the lipid matrix naturally without synthetic surfactants, through reverse engineering study by column chromatography and HPTLC analysis. The composition of fatty acid with the presence of short chain and medium chain triglyceride fraction in cow ghee along with natural existing phospholipids serves as the physicochemical basis for spontaneous nanoemulsification when diluted in the aqueous phase. Three main strategies for modernization by nanotechnology are considered: SNEDDS (reformulation for oral delivery systems); nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLPs) for topical systems; and nanoemulgel systems for the delivery systems for wounds and skin. The results show therapeutically significant improvement from the perspective of measurable improvements over conventional ghrita and preclinical evidence exists in all three domains: CNS, wound healing, metabolic, and anti-infective. The

discussion covers three future directions: designing formulations using computational tools, metabolomics-based standardization, and future directions using solid-SNEDDS platforms, coupled with regulatory issues and quality by design approaches.

KEYWORDS: Ayurvedic medicine, bioavailability enhancement, ghrita, lipid-based drug delivery systems, nanostructured lipid carriers, self-nanoemulsifying drug delivery systems.

INTRODUCTION

According to the World Health Organization, some 80% of the world's population depend on traditional medicines for some part of their primary health care needs, among which Ayurveda is one of the most well documented and generally used traditional medicine systems.[1] Lipid based preparations are of outstanding importance in Ayurvedic pharmaceuticals as described elaborately in various classical herbal/pharmaceutics books such as Ayurvedic foundation classical texts, Charaka samhita of Charaka, Sushruta samhita of Sushruta and Ashtanga Hridaya of Acharya Vagbhata, which is more than 3000 years old.[2] These formulations were principally in the form of ' Medicated Clarified Butter' (ghrita) and ‘Medicated Oils’ (taila) and not only formulations used for the transportation of the botanical actives but evolved as highly developed, pharmaceutical formulations in which the lipid matrix was used not only as an extraction medium but also acted as a route adaptive mode of delivery as well as a stabilizing base and absorption enhancer.[3]

Ayurveda says that ghrita is able to absorb all the therapeutic principles of co-processed substances without losing its own properties this is something that the science of the pharmaceutical has yet to be quantified. The paradox in this review is that preparations of Sneha Kalpana, in substance, one of humanity's oldest empirically derived lipid based formulation devices (LBDDS), but are virtually completely ignored in the mainstream pharmaceutical literature on LBDDS, nanotechnology and formulation science.[4] Consequential absence. lipophilic platforms such as simple oil solution or self nano emulsifying drug delivery system (SNEDDS) have been developed by contemporary pharmaceutical science to overcome the poor bioavailability observed for approximately 40% of the existing drugs and over 90% of the new chemical entities that are not classified into high to medium or high bioavailable categories according to the Biopharmaceutics Classification System. Simultaneously, the intricate natural active molecules found in Ayurvedic ghrita formulations, which are mostly terpenoids, limonoids, and triterpenoids and

contain very low water solubility properties, show exact the type of phytomolecules for which lipid-based nanotechnology has proven to demonstrate formulation benefit.[5]

There have been no systematic studies of the convergence of these two streams of research. Reverse engineering studies have shown that polar active botanicals are transferred to the lipid base even in the absence of synthetic surfactant into the making of ghrita, Paka and ghritakarma formulations of classical preparations, a classical preparation Guggulu Tiktaka Ghrita showed monophasic liquid result and with evidence of micro- and nano-vesicular entrapment. The results here clearly indicate that classical ghrita preparations spontaneously create colloidal dispersions like those obtained by the modern chemical formulation techniques such as self-emulsifying and nanoemulsion and the pharmaceutical know-how contained within these ghritas require serious scientific study in the light of modern formulation science.[6] The review critically investigates the basic principles related to the making of lipid formulations in Ayurveda, correlates them with the existing LBDDS classification and compares the basic mechanisms of both Paka process and Nano emulsification. It then explores the nanotechnology-based modernization options most relevant to these preparations, talks about formulation design challenges in multi-component herbal formulations, examines the therapeutic evidence for the nano preparations of Ayurvedic lipid formulations, and explores regulatory and translation considerations that determine the path from traditional to validated pharmaceutical preparation. The final goal is to identify that lipid based dosage formulations or lipid products based on the principles of Ayurveda are not empirically backward forerunners of modern pharmaceutical industry, but are a well optimized dosage system and can write a new success story with nanotechnology.[7]

AYURVEDIC LIPID FORMULATIONS: SNEHA KALPANA AND THE PHARMACEUTICAL SCIENCE HIDDEN IN TRADITION

The word Sneha means attachment or unification and is then used for oleaginous substances, both plant and animal, both of which in pharmaceutical terms predict the application of lipids as a functional delivery medium, vs. just a vehicle. On the basis of canonical Sharangdhara Samhita, the Ayurvedic pharmaceutical detail, Sneha Kalpana is a category of oleaginous medicines, which has been precisely described as the preparation of the medicine using the combination of kalka (small herbal paste), sneha (oil/lipid base) and drava dravya (liquid base, in most frequently mentioned cases - kasaya or herbal decoction) in the standard proportion in which each ingredient is added to the base.[8] This proportion is not determined

at random as it represents an empirical ratio that was found in such a way, that during the Paka process adequate aqueous phase to facilitate the mass transfer of polar solutes into the lipid medium, and adequate lipid phase to directly extract solutes classified as non-polar phytoconstituents takes place.[9]

This preparation is done in three stages: Sneha Murchana (pre-processing of the lipid base), Sneha Paka (thermal extraction and phase transfer), Paka Siddhi (performed by endpoint testing). In modern terms, the ‘pre-treatment step' for cow ghee (murchana), upon which it is formulated, has a pharmaceutical rationale that is just beginning to be recognized. The process requires the raw ghrita to be heated with particular herbs in a prescribed ratio, and is meant to purify Amadosha (unrefined impurities), eliminate Durgandha (bad odour) and remove Ugrata (sharpness), while generating the Virya (potency) of the base. From the analytical point of view, the work published so far has established that in addition to sustaining the ratio of unsaturated to saturated fatty acids in ghrita, the herbs of the Murchana are also known to have antioxidant and anti-lipid peroxidation activity which protects the ghrita base from primary oxidation during subsequent processing of Paka.[10] It is conceptually similar to recent excipient conditioning processes in lipid formulation development in which the lipid base is subjected to preliminary treatment to enhance its emulsifying properties and drug substance-lipid interactions. There are 5 distinct identifiable stages in the Paka (boil) process which include Amapaka, Mridupaka, Madhyamapaka, Kharapaka and Dagdhapaka that involve variations in the physical appearance of the kalka and the physical changes of the mixture. Madhyamapaka is recommended to be distilled at the point approximately 83–102°C with controlled heat (mandagni) for 2–3 days, after this, the calka gets non-sticky, loses cracking sound when tested on flame, ghrita bubbles fade and lasts to get its typical color, odor and flavor. Important, however, is that classical texts caution against proceeding to Kharapaka for oral preparations as overheating past Madhyamapaka involves the degradation of phytoconstituents and a change in palatability a warning that pharmaceutical scientists recognize today as being about thermolabile actives and thermal decomposition products.[11]

The most important finding in the pharmaceutical research area came about after reverse engineering ghritas with the use of column chromatography and combination of normal and reverse phase HPTLC analysis of Guggulu Tiktaka Ghrita (GTG). In this study, it has been shown that all the active botanical ingredients found in GTG had a polar nature and they were

present in the minor fraction (22.49% extractive value) representing the dissolved and dispersed botanical ingredient in the lipid matrix.[12] Nonpolar fraction of petroleum ether (75.60%) did not contain any active botanical ingredient on HPTLC. As the aqueous phase is fully removed from the oil during Paka and no synthetic surfactant is introduced, conclusion was drawn that the polar actives are found in a micro-/nano-vesicular form in the oil matrix and is considered as direct evidence of the generation of a colloidal dispersion system in the absence of external emulsification technology to make an Ayurvedic ghrita preparation. Classical Sneha Kalpana formulations brim with therapeutic scope across entire ambit of clinical medicine as demonstrated in Table 1.[13] Brahmi Ghrita is a classical formulation prepared with Bacopa monnieri, Acorus calamus, Convolvulus pluricalis and Saussurea lappa used orally using Snehapana as indicated in Neurological conditions such as Apasmara (epilepsy) and Unmada (psychosis). Jatyadi Ghrita is formulated from a complicated polyherbal (Jasminum officinale) ghee base to be used topically for the management of wounds. Topical application of Jatyadi Ghrita showed significant reduction in wound area after 42 Days (92%) compared to irradiated controls with the associated decrease in bacterial load, inflammatory cell infiltration, and expression of TGF-β1, similar to the results of mupirocin HCl in standard wound models. Triphala Ghrita is well established with eye and gut indications and Kalyanaka Ghrita with psychosomatic disorders. The versatility of Sneha Kalpana as a delivery system, i.e., delivered orally (Snehapana), topically (Abhyanga), nasally (Nasya), or rectally (Basti), can be attributed to an ancient understanding in Classical pharmacy that lipid carriers could provide route adaptive benefits that could not be achieved using other traditional dosage forms.[14]

TABLE 1: Comparative Overview of Classical Ayurvedic Sneha Kalpana Formulations Composition, Preparation Parameters, Therapeutic Indication, Administration Route, and Modern LBDDS Analogues.[15,16]

Formulation	Key Active Botanical Ingredients	Paka Stage for Use	Therapeutic Indication	Primary Route	Modern LBDDS Analogue
Brahmi Ghrita	Bacopa monnieri, Acorus calamus, Convolvulus pluricalis, Saussurea lappa	Madhyama Paka	Neurological epilepsy (Apasmara), psychosis (Unmada); cognitive decline	Sneha Pana (oral)	Lipid nanoparticle / nano emulsion for CNS delivery
Jatyadi Ghrita	Jasminum officinale, Azadirachta indica, Curcuma longa, Rubia cordifolia, Glycyrrhiza glabra	Khara Paka (topical)	Wound healing, skin ulcers, burns, radiation wounds	Topical (Abhyanga)	NLC-based nanomole / SNEDDS topical gel
Triphala	Terminalia chebula,	Madhyama	Ophthalmic disorders;	Oral; Ocular	Microemulsion / lipid

Ghrita	Terminalia bellirica, Emblica officinalis, Go-ghrita	Paka	GI conditions; rejuvenative	drops	vesicle
Kalyanaka Ghrita	28-herb polyherbal complex including Nymphaea stellata, Santalum album, Shorea robusta	Madhyama Paka (85°C, 3 days)	Psychosomatic disorders-schizophrenia (Unmada), epilepsy (Apasmara)	Sneha Pana (oral)	SNEDDS for multi-phytoconstituent oral delivery
Guggulu Tiktaka Ghrita	Commiphora mukul (Guggulu), Azadirachta indica, Tinospora cordifolia, Adhatoda vasica	Madhyama Paka	Inflammatory conditions, deep-seated ulcers, gout, cardiac diseases	Oral; Topical	Nanoemulsion / lipid nanocarrier
Mahanarayan Taila	Asparagus racemosus, Withania somnifera, sesame oil base + 50+ herb complex	Khara Paka	Neuromuscular conditions, Vata disorders, joint pain	Topical (Abhyanga); Basti	NLC / SLN-based transdermal delivery system

LIPID-BASED DRUG DELIVERY SYSTEMS: THE MODERN COUNTERPART

The rational design of lipid-based formulations for oral and topical drug delivery became codified when Pouton introduced the Lipid Formulation Classification System (LFCS) in 2000, subsequently revised in 2006 to include a fourth formulation type. The LFCS has categorized the lipid formulations on the basis of their composition, polarity, and need for dispersion after gastrointestinal digestion into four types.[17] Type I formulations are simply digestible triglycerides and do not contain any surfactant, utilising the intestinal lipolysis to provide the digestate needed to create the colloidal dispersion so that the drug can be delivered to the absorptive surfaces – this class of formulations includes the vitamin D analogs and retinoids currently marketed in softgel capsules. In the type II systems, they use oils in conjunction with water-insoluble surfactants (HLB < 12) and form emulsions with droplets that are in general larger than 250 nm when released from an aqueous medium and are also called self emulsifying drug delivery systems (SEDDS).[18] Type IIIA and IIIB formulations are created using hydrophilic surfactants and cosolvents, resulting in even smaller nanodispersions; Type IIIA droplets are in the range of 50 to 250 nm, and Type IIIB are in the sub-50 nm range, most of the existing lipid formulations marketed are of Type III. Type IV systems use only surfactant/cosolvent with no lipid containing matrix for drug dissolution; these systems allow for the smallest resulting particle size but also have the greatest likelihood of drug precipitation after the aqueous injection due to the loss of the oil matrix used for drug dissolution.[19] The LFCS framework shown in figure 1 offers an organising schema for positioning classical Ayurvedic ghritas while taking into account their spontaneous emulsification behaviour and Oil/Surfactant Equivalent ratio. Of the various

nanosystem platforms which are relevant in the modernization of lipid-based formulations of ayurvedic medicines, SNEDDS are very pivotal. SNEDDS are isotropic mixtures of oil, surfactant and cosurfactant, which can spontaneously form fine nanoemulsions of the oil phase in water (oil in water, < 100–200 nm) upon gentle agitation with aqueous media, without applying energy to the mixture. Phytoconstituents have multiple pharmaceutical benefits associated with their use such as keeping the drug in a dissolved nanodispersed state during passage through the stomach, improving gastrointestinal tract permeability by facilitating the lymph absorption via chylomicron incorporation, inhibiting P-glycoprotein (PGP)-dependent efflux through specific interactions with surrogate molecules (surfactants) found in the excipients, and protecting labile phytomolecules against enzymatic and chemical degradation in gastrointestinal lumen.[20] Although compound and formulation specific, published studies have shown that the bioavailability enhancement ratio for SNEDDS with lipophilic BCS Class II or IV drugs range from about 1.5- to 8-fold when administered as SNEDDS compared with conventional oral formulation. SLNs were invented by Müller in 1991 which are simply solid lipid nanoparticles (miniscule particles with the solid form of lipids) stabilized with surfactant and of particle size range from 50 nm to 1000 nm. The benefits that they offer for phytoconstituents are their physical and chemical stability, their controlled release kinetics and the preparation process (high-pressure homogenisation) designed to be scalable. SLNs have a drawback in that the lipid backbone is forced to undergo polymorphic transitions during storage processes, leading to expulsion of the drug; this is where nanostructured lipid carriers (NLCs) came into the picture to alleviate and avoid this problem. The solid and liquid lipids are combined into the NLCs, resulting in an imperfectly crystalline or amorphous bulk of lipids that allows for a higher drug loading capacity, which also withstands drug expulsion during long storage.[21] The other added advantage of NLCs is the ability to form an occlusive film on the skin surface, facilitating penetration through the stratum corneum (SC) and giving long-lasting and controlled release of the encapsulated active. Based on the large amount of preclinical evidence supporting their use in multiple drug administration routes, a 2024 Expert Opinion on Drug Delivery review confirms the incorporation of plant derived bioactives in SLNs and NLC could be an attractive option to boost their in vivo bioavailability. For any formulation modernization project based on the Ayurvedic formulations, selection of these platforms must be governed by the physicochemical characteristics of the major phytoconstituents, route of administration and the controlled release desired; just as Sneha Kalpana was responsible for based on the output of a given route of administration, such as the differences in Paka stage.[22]

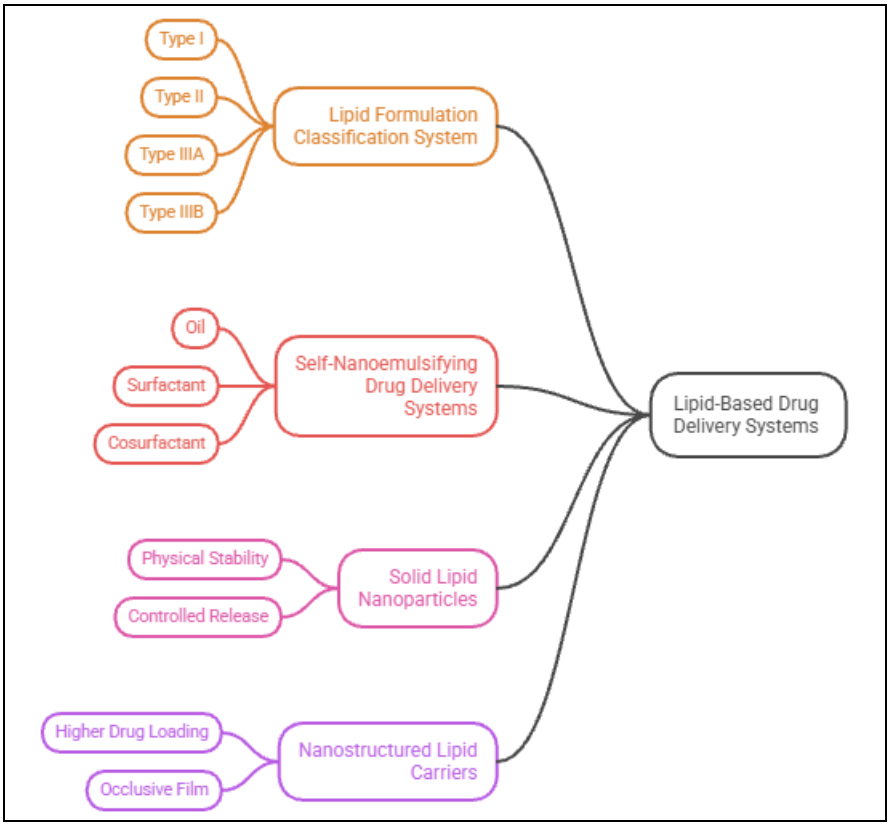

Figure 1: Lipid-Based Drug Delivery Systems: Modern Counterparts.

MECHANISTIC CONVERGENCE: WHY GHRITA IS A NATURAL SELF-EMULSIFYING SYSTEM

The known composition of cow ghee and the physicochemical consequences of the Paka process support the mechanistic argument that ghrita is a naturally arising system of nonpolar self-emulsifying systems and the results of reverse engineering studies provide direct analytical evidence to support this. Cow ghee is a mixture of total lipid, about 98%, of which the saturated fatty acids vary in amount from 55 to 70% and monounsaturated fatty acids are about 20 to 25%. In the saturated fraction, palmitic acid (22–38%), stearic acid (8–19%) and myristic acid (6–13%) are the major components, whereas the dominant monounsaturated fraction is oleic acid (19–32%) with the presence of considerable amount of short-chain and medium-chain fatty acids (butyric acid is C4:0 and has been estimated to be 1-5%, caproic acid is C6:0, caprylic acid is C8:0, capric acid is C10:0), also.[23] Besides, the gross composition consists of diglycerides (1-2%), monoglycerides (0·1–0·2%), free fatty acids (1–10 mg/100 mg) and phosphosphingolipids to 80 mg/100 g, fat-soluble vitamins A, D, E and K and naturally occurring sterols. This compositional profile is of pharmaceutical relevance and, in general, medium chain triglycerides (C8–C10) are regularly seen as the class of lipids most suitable for being emulsified to fine dispersions (less than 200 nm) by the application of

nonionic surfactant. In the case of the medium chain triglycerides in medium chain triglycerides (MCTs), the use of this functional ingredient in ghee, but not in the other long-chain oils, will also supply an inherent property of emulsification. Further, the phospholipid fraction found in ghee (even in minute quantities) naturally possesses an HLB range (around 7 to 10) which can reduce interfacial tension at oil–water interface, and make submicron dispersions without the need to place a synthetic surfactant in the dispersion.[24]

This basic lipid profile is altered with the Murchana pre-treatment stage, which has an influence on the behavior of self-emulsification directly. Based on analytical comparison of plain ghrita with Murchita Ghrita it is found that the proportions of unsaturated fatty acids to unsaturated fatty acids remained the same and the solubility pattern and absorption pattern of the final formulation were changed in Murchita Ghrita. Herbs added during Murchana (Phyllanthus emblica, Curcuma longa and Cyperus rotundus) mustard contain polyphenols, which act as antioxidants and lower the effect of high temperatures during the Paka, to help protect the oleic acid and poly unsaturated fraction from oxidative degradation. Physicochemical result is a lipid base with modified free fatty acid profile, improved oxidative stability and altered characteristics of surface activity which collectively control the rate and extent of spontaneous nanoemulsification when contacted with aqueous media.[25]

The thermodynamic driving force for the phase transfer of polar actives into the lipid matrix is offered by the Paka process itself. The aqueous phase will gradually be evaporated as the kasaya (16 parts) and ghrita (4 parts) mixed with kalka (1 part) is first heated at Madhyamapaka temperature (about 83–102°C). Mass transfer of the dissolved polar phytoconstituents is driven by the same thermodynamic processes as would be simulated by solute transfer during pharmaceutical co-processing and/or hot-melt extrusion, with the concentration gradient due to this evaporation process maintaining Fickian diffusion of the dissolved components from the aqueous phase to the lipid phase of the product.[26] However, once the aqueous phase has completely disappeared the polar actives that were solubilised in the kasaya become "trapped" in the lipid phase and the result is a monophase product in which no phase separation is apparent, meaning that the polar species must now be in a nano-dispersed or vesicularly enclosed form within the oil. The same was observed during reverse engineering of Guggulu Tiktaka Ghrita as all active botanical ingredients were polar and minor fraction (contain 22.49% of total) was polar fraction in which all active biomarkers

were identified, while non-polar lipid fraction (contain 75.60% of total) contained no bioactives.[27]

The analogy with the modern SNEDDS is thus straightforward as shown in Figure 2. Both systems are induced by a lipid basis and contain actives which are only slightly soluble in the phase with which they interact and create a fine colloidal dispersion when exposed to aqueous media via a thermodynamic self-emulsification process. Whereas the difference is the method employed in the SNEDDS process (solubility screening and pseudo-ternary phase diagram construction to get SNEDDS with the desired nanodroplet size and therapeutic stability against precipitation), in the classical ghrita process, empirical optimization over many years has selected the excipients that produce functional outcomes along with the lipid base and processing conditions that yield them [28]. The critical difference is that Ayurvedic ghrita doesn't contain the hydrophobic hydrophilic synthetic surfactant in the form of cremophor EL or Tween 80 or Labrasol which is used in SNEDDS to satisfy Type IIIA performance, thus the Ayurvedic ghrita is essentially a Type I–II equivalent system by LFCS criteria; the Murchana-modified phospholipid fraction is also partially hydrophilic, thus providing a partial emulsification function. Nanotechnology based modernization is exactly what can fill this gap between empirically competent and pharmaceutically optimized.[29]

Incorporating ghrita orally also has a lipid-mediated absorption benefit which is consistent with the mechanisms of absorption of LBDDS. In the small intestines, pancreatic lipase degrades triglycerides to monoglycerides and free fatty acids which together with bile salts form the mixed micelles which act as solubilising vehicles for co-delivered actives. In particular long chain lipids have been found to be effective for the induction of the lymph transport of the co-delivered drugs since they activate the formation of chylomicron, directly avoiding hepatic first-pass metabolic clearance. Ghrita consists of a blend of short-chain, medium-chain and long-chain fatty acids, all of which stimulate the three pathways of absorption simultaneously micellar solubilization, enterocyte absorption and lymphatic transport. Further, lipid based formulations when made in systemically go across the blood brain barrier due to lipid-mediated free diffusion along with receptor-mediated transport and are the basis of the classical therapeutic application of ghrita preparations in neurological conditions such as Brahmi Ghrita.[30]

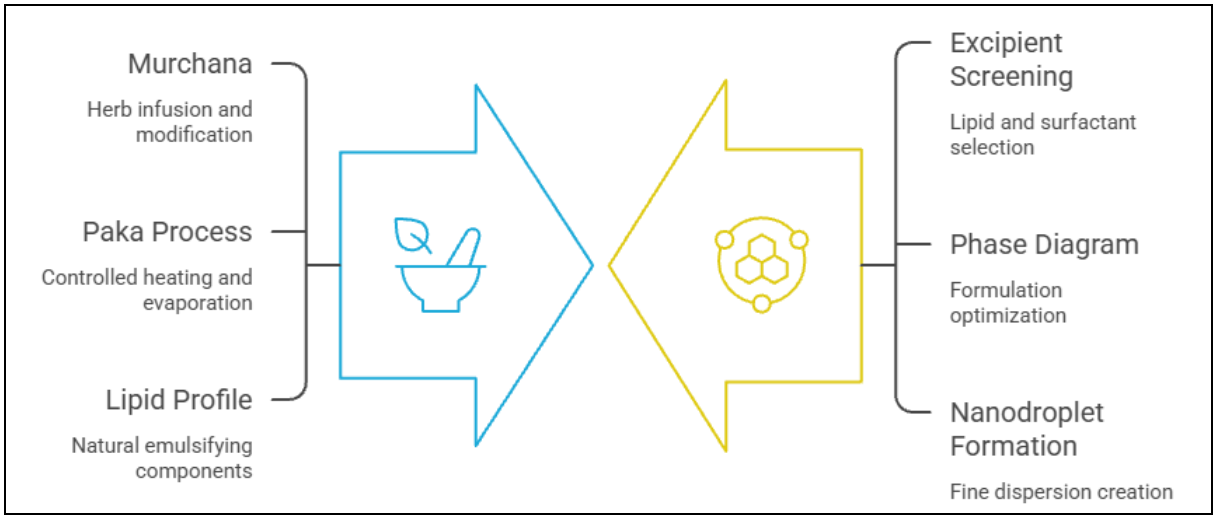

Figure 2: Ayurvedic Ghrita and SNEDDS: Convergent Self-Emulsification.

NANOTECHNOLOGY-BASED MODERNIZATION STRATEGIES FOR AYURVEDIC LIPID FORMULATIONS

SNEDDS Reformulation for Oral Ayurvedic preparations. The most direct approach towards modernisation of oral ghrita preparations involves addition of lipid base of traditional ghrita as the oil phase component of an SNEDDS along with pharmaceutically approved surfactants and cosolvents which will take the system from type I–II to type IIIA self-nanoemulsifying platform. This is a practice that has its roots in the real world. The blackish color of the fixed oil was completely dissolved within 10 minutes without any pH change by the published SNEDDS formulation of Semecarpus anacardium Linn. fixed oil in the ratio 10:60:30% w/w (Labrafil M1944CS: Tween 80: Transcutol P) and the formulation was stable and reproducible for a period of 3 months.[31] The preparation of SNEDDS using classic ayurvedic ghritas and supplementary lists of active ingredients from the literature, such as curcumin, guggulsterone and ellagic acid, has been shown to achieve significant enhancements in dissolution and bioavailability, for example, curcumin-piperine combination SNEDDS containing black seed oil as the active ingredient oil phase: SNEDDS droplet size was below 100 nm, which resulted in drug release of curcumin and piperine by 60% and 77% respectively as compared to significantly lower drug release from conventional formulations. These results validate that the ghrita lipid base, when combined with modern surfactant and cosolvent excipients in specific SNEDDS ratios, constructed by the pseudo-ternary phase diagram enables the creation of pharmaceutical grade nanoemulsion systems, that are much more effective than those that are conventionally prepared using only the surfactant. The phospholipid complex approach is an important intermediate step between the amphiphilic

situation and the SNEDDS formulation for the Ayurvedic phytoconstituents that have polar phenolic and terpenoid that cannot be solubilized in a completely lipid matrix. In this technique, the phytoconstituent is first reacted with the phosphatidylcholine in an aprotic solvent to form the lipophilic complex which is then more easily made into a SNEDDS-compatible payload: the technique was validated for ellagic acid, using a phospholipid-complexed SNEDDS with a mean globule size of 106 nm and ex vivo permeability significantly enhanced compared to the free acid.[32]

Topical Ayurvedic taila and ghrita platforms of NLC and SLN platforms. Topical formulations represent another modernization trajectory, focusing on increased skin penetration, dermal residence time, and sustained drug release (as opposed to systemic bioavailability) of topical Ayurvedic products like medicated taila and Jatyadi Ghrita for wound care, skin disorders, and musculoskeletal diseases. The NLCs offer some special advantages for this purpose. The Franz diffusion cell and porcine ear skin studies have revealed that the skin permeation of NLC-loaded curcumin and NLC-loaded thymol gels were both higher than the conventional nanoemulsions and the steady-state release was achieved by both NLC formulations, respectively, after 72 hours and 12 hours in skin. SLN formulations (not niosomes) of *Withania somnifera* actives delivered withaferin A and withanolide A to the stratum corneum-epidermis and epidermis-dermis layers of skin, while only SLN formulations (not niosomes) provided skin penetration to the deeper dermis layer to achieve anti-inflammatory activity at subcutaneous targets. Particles size of 147.9 nm, entrapment efficiency of 89.99% and in vivo wound healing in Wistar rats which showed reduced healing time and accelerated wound closure as compared to control; *Withania somnifera* NLC optimized with central composite design proved to be successful in delivering the topical delivery of Ayurvedic phytoconstituents by utilizing NLC platform.[33]

Educating about Nanoemulgels and Nano-Organogels as the Modern-day dosage forms. The third approach keeps the emollient, occlusive, and tissue penetrating properties of the classical lipid formulations and adds the nanoparticulate drug delivery properties of the semi solid gel matrix. The physical stability, controlled release and patient acceptability of a gel base are combined with the advantages of the nanoemulsion (submicron droplet size, enhanced interfacial area and thermodynamic driving force for the penetration of the membrane) to create nanoemulgels. This platform is especially interesting in the case of Ayurvedic preparations formulated for topical application in wound healing and dermal

delivery as seen in the case of a full-thickness excision rat wound healing study comparing an optimized SNEDDS formulation of the seed oil (DROPLAN-50.02 nm) to the unformulated seed oil, where the optimized seed oil showed enhanced wound area reduction, increased hydroxyproline skin content, improvement in Col1A1 mRNA expression, and significantly higher VEGF skin expression, all of which indicate that the topically applied seed oil showed increased wound healing efficacy with enhanced anti-inflammatory, pro-collagen, and pro-angiogenic mechanisms when nanoemulsified. The results of these three strategies are summarized in Table 2 along with the published formulation parameters and outcomes.[34]

TABLE 2: Published Preclinical Studies on Nano-Modernized Ayurvedic or Herbal Lipid Formulations Phytoconstituent/Active, Nanoplatform, Key Formulation Parameters and Reported Therapeutic/Bioavailability Outcome[35,36]

Phytoconstituent / Active	Traditional Source / Preparation	Nanoplatform	Key Parameters	Reported Outcome
Fixed oil of Semecarpus anacardium	Bhallatakadi Taila (Ayurvedic)	Liquid SNEDDS	F19: Labrafil M1944CS/Tween 80/Transcutol P (10:60:30% w/w); droplet size within nanometric range	100% oil dissolution within 10 min, pH-independent; stable 3 months
Curcumin + Piperine	Turmeric/black pepper- common Ayurvedic ghrita additives	Bioactive SNEDDS (black seed oil base)	Black seed oil/Imwitor 988/Transcutol P/Cremophor RH40 (20:20:10:50); solidified with Neusilin	Curcumin and piperine release 60% and 77% respectively; amorphous state confirmed
Withaferin A + Withanolide A	Ashwagandha (Withania somnifera)-Balashwagandhadi Ghrita	SLN (particle size 165.9–304.6 nm)	50% ethanol extract SLNs; Franz diffusion cell, porcine ear skin	Dermis and epidermis penetration achieved; superior to niosomes for deeper skin delivery
Withania somnifera extract (withanolides)	Ashwagandha-Ayurvedic wound healing preparations	NLC (central composite design)	Particle size 147.9 nm; entrapment efficiency 89.99%; PDI 0.173; Carbopol 940 gel base	89.66% drug release at 12 h; reduced wound healing time in Wistar rats in vivo
Opuntia ficus-indica seed oil	Traditional herbal wound healing oil (SNEDDS modernization model)	SNEDDS	Tween 20/PEG 200/OFI oil by D-optimal mixture design; droplet size 50.02 nm	Superior wound area reduction; increased hydroxyproline, Col1A1 mRNA, VEGF and TGF-β expression vs. unformulated oil in rats
Ellagic acid (phospholipid complex)	Pomegranate-derived polyphenol in Ayurvedic formulations	SNEDDS of phospholipid complex	Mean globule size 106 nm; cloud point 83–85°C	Improved ex vivo permeability; enhanced dissolution vs. free acid

FORMULATION DESIGN CONSIDERATIONS FOR MULTI-COMPONENT AYURVEDIC SYSTEMS

The formulation science challenges of the modernisation of a classical ghrita to a validated nanoformulation are qualitatively different from those for a single-API SNEDDS or NLC

system. However, a ghrita like Brahmi Ghrita contains at least four to five distinct botanical ingredients, each with a complex phytochemical profile comprised of several molecules with varying polarity, solubility and stability under thermal and excipient stress; and none of these ingredients is a single, defined ingredient. Unlike the conventional pharmaceutical SNEDDS formulation development, constraints are imposed at every stage of formulation development of this multi-component reality.[37]

The first problem is the selection of excipients. Most classical SNEDDS screening is based on the equilibrium solubility of the API in a series of excipients (lipid), surfactants and cosolvents and subsequent construction of a pseudo-ternary phase diagram to determine a possible nanoemulsification region. There are dozens of constituents in the active part of the formulation in the form of a polyherbal extract and hence, a single API is not used, but representative marker compounds are used for solubility screening that are chosen based on their documented pharmacological relevance and chromatographic detectability. The use of a single marker for a multi-active preparation or the use of inappropriate markers introduces systematic error into the formulation development process, which is based on solubility, potentially with a formulation which is optimized for one active and subtherapeutic for the others. Published compatibility studies of polyherbal formulations have revealed that it is possible for chemical interactions between various active markers of different botanical sources and the excipients to occur at accelerated stability conditions (40 °C / 75 %RH) which can affect solubility, uptake and therapeutic response; this risk is increased in lipid formulation systems in which the excipients (oil) form a thermodynamically active matrix, where there is a concentration of reactive Phyto molecules.[38]

The QbD framework is outlined in the ICH Q8–Q11 guidelines and has increasingly been adopted in the development of herbal formulations and is a structured approach to dealing with these challenges. In Ayurvedic SNEDDS development, Quality Target Product Profile (QTPP) shall at the same time meet with the following requirements of the classical ghrita base as per Ayurvedic Formulary of India along with the modern pharmaceutical specifications for the nano formulation: Droplet size (≤ 200 nm), polydispersity index (≤ 0.3), zeta potential (+/- 30 mV or greater) and encapsulation efficiency (%). Identification of critical quality attributes (CQAs) of the nanoformulation component of such a system should be performed by applying risk assessment methods like Ishikawa diagrams and Failure Mode Effects Analysis, specifically to the multi-ingredient context. The Box-Behnken design

(BBD), D-optimal mixture design, and Central Composite Design (CCD) are the most suitable statistical designs for optimizing multi-variable SNEDDS systems, as they enable the characterisation of interaction effects between different variables, such as oil concentration, surfactant-to-cosurfactant ratio, drug/extract loading and process temperature, which would be impossible to assess by one factor at a time experimentation.[39]

A recently published review that combined the QbD and in silico approaches for the development of SNEDDS has revealed that DoE-based formulation development can greatly minimize the need for trial-and-error to identify critical formulation factors, can more accurately estimate the interactions between formulation variables and can enhance the reproducibility of optimized SNEDDS formulations, which are essential for SNEDDS containing multiple components as part of the herbal payloads and where significant variations in the botanical raw material must be compensated at the formulation development stage. The important additional capability for solid-state characterization with a solid-state thermal analysis technique such as differential scanning calorimetry (DSC) for assessment of drug-excipient compatibility, and X-ray powder diffraction, for determination of polymorphic state of any co-processed solid fractions, is equally important in confirming that complex botanical actives are dispersed in an amorphous or molecularly dissolved state within the lipid matrix.[40]

TABLE 3: Critical Formulation Variables for SNEDDS Optimization and Their Translation to Multi-Component Ayurvedic Systems.[41,42]

Formulation Variable	Effect on Single-API SNEDDS Performance	Translational Challenge for Ayurvedic Multi-Phytoconstituent Systems
Oil type and concentration	Determines drug solubilizing capacity; MCTs produce finer droplets than LCTs	Must solubilize a range of phytomolecules with divergent polarities; single oil may underperform for polar actives
Surfactant HLB value	Controls spontaneous emulsification behavior; HLB >12 required for Type IIIA systems	Natural phospholipids in ghrita provide HLB ~7–10; synthetic surfactants must augment, not destabilize, this baseline
Surfactant: cosurfactant ratio	Defines nanoemulsification region in pseudo-ternary phase diagram	Ratio must be screened against multiple marker compounds simultaneously to ensure co-encapsulation across polarity spectrum
Drug/extract loading	Excess loading reduces encapsulation efficiency and increases droplet size	Maximum loading differs per phytoconstituent; polyherbal extract loading must balance total solids with nanoemulsion stability
Aqueous dilution factor	Progressive dilution during GI transit triggers nanoemulsification	Phase behavior under simulated GI fluid dilution must be validated using both simulated gastric and intestinal media

Paka temperature (thermal processing)	Not applicable in modern SNEDDS (mixed at ambient/mild temperature)	Classical thermal extraction at 85–102°C degrades heat-sensitive actives; modernization must decouple extraction from formulation steps
Solid state of active	Amorphous dispersion within lipid matrix preferred for maximum dissolution rate	DSC and XRPD confirmation of amorphous or molecularly dispersed state for multi-constituent extract essential for bioavailability projection

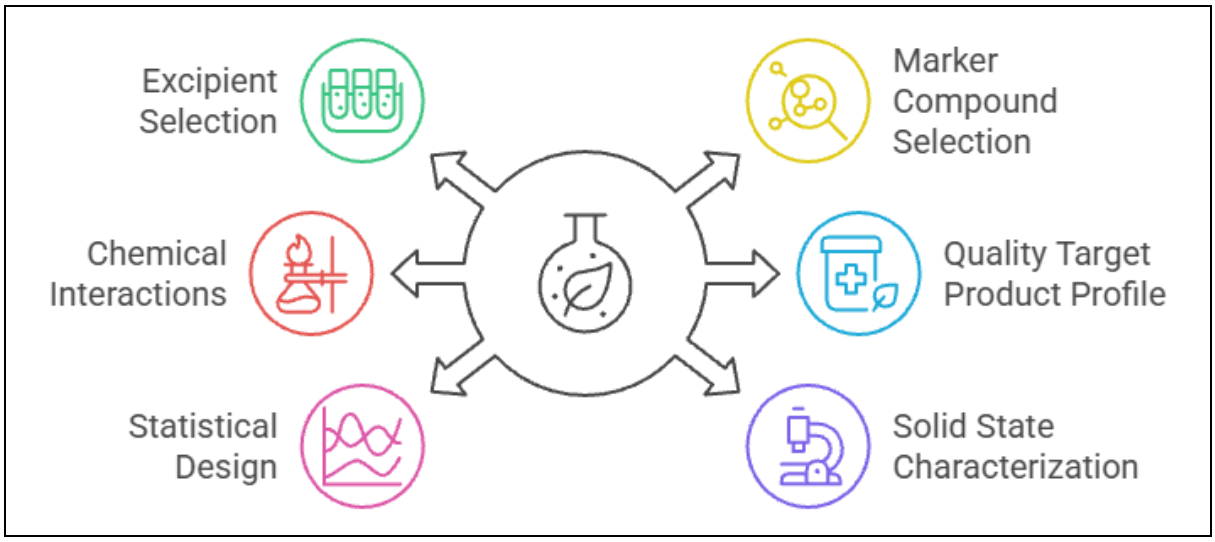

Figure 3: Challenges in Modernizing Ayurvedic Formulations.

Therapeutic Applications and Preclinical Evidence

The therapeutic evidence base for the ayurvedic lipid formulations, in their main disease domains, shows a clear pattern: though the classical ghrita formulations have proven to have reproducible pharmacological activity in preclinical models, a comparison of a ghrita or its phytoconstituent base, which is once again nanotechnology reformulated, and its ayurvedic counterpart shows the magnitude of the enhancement that can be achieved by the use of nanotechnology based reformulation. The most interesting and research-rich space to modernize ghritta is the CNS domain. Brahmi Ghrita is described in various Ayurvedic texts of the FDAI, and it has shown to have neuroprotective and cognitive enhancing properties in animal studies such as scopolamine-induced amnesia studies, in which it was found to significantly enhance learning behaviour and memory retention than the control. Oral treatment with the preparation resulted in significant reduction of microglial proliferation, microglial activation, immunohistochemical markers of Iba-1, GFAP and reduced expression of MHC-II in hippocampus and cerebral cortex in rats with experimentally induced neuroinflammation using Poly I:C infusion into the cerebral ventricles.[43]

The mechanism of entry of ghee into the CNS is well known, and the Bacopa monnieri extract's active constituents, the bacosides A and B, have been shown to induce dendritic growth, enhance synaptic transmission and inhibit acetylcholinesterase, a result verified in a 52-week randomised study, which produced statistically similar results as donepezil (10 mg) in patients with Alzheimer's disease and mild cognitive impairment. Nanotechnology-based modernization will be clinically relevant as the use of nanodroplets below 100 nm, which is more efficient in crossing the BBB compared to the conventional preparation, will further broaden this pharmacological profile to patients with the requirement for BBB targeted delivery where the conventional preparation does not perform optimally. Guggulu Tiktaka Ghrita has the most substantiated pharmacological profile for metabolic and anti-inflammatory conditions. In dyslipidemic Wistar rats fed a high-fat diet, GTG treatment for 21 days resulted in statistically significant decreases in blood glucose, serum total cholesterol, LDL cholesterol and VCAM-1 (elevated VCAM-1 is a marker of early atherosclerotic inflammation) when compared to untreated rats.[44]

Their hypolipidemic, hypoglycemic, anti-inflammatory properties are mainly due to guggulsterones E and Z, which act as nuclear receptors modulators such as farnesoid X receptor (FXR) that regulates cholesterol metabolism and bile acid synthesis. The lipid nature of ghrita is essential for these actions: In Ayurvedic pharmacology it has been firmly established that ghuggulu is poorly absorbed in the absence of lipid vehicle, and ghuggulu emulsified in ghrita during the process of Paka is directly found to increase the solubilisation and absorption of ghuggulu in the intestine. Bioavailability of guggulsterone would be expected to be even higher, if the classical preparation is reformulated as a SNEDDS or NLC system; the lipid matrix of the classical preparation would be used as an oil phase and the defined lipid matrix would be used as a surfactant phase. In addition, the application of the lipid vehicle of Triphala Ghrita in ophthalmic conditions such as a published randomised comparative clinical trial on the use of Tarpana therapy for dry eye syndrome (Shushkakshipaka) is a unique delivery route, the ocular surface, for which the lipid formulation offers an additional corneal penetration advantage which an aqueous formulation does not.[45]

The versatility of ghrita-based preparations in multiple routes of administration is demonstrated in this example, a trait that should be taken into consideration when designing dosage forms for ghrita-based preparations suitable for administration by other routes such as

the eye, nose or rectum, as mentioned in classic Sneha Kalpana literature. The main reason for the lipid formulations of Ayurveda to be used for anti-infective purpose is that the minimum inhibitory concentration of the phytomolecules present in it like Nimbin, Nimbolide etc. of Azadirachta indica of formulations like Guggulu Tiktaka Ghrita is enhanced with the help of encapsulation in lipid nanocarriers as is summarized in Figure 3. In all these fields, a common scientific conclusion is that the classical ghrita preparations show genuine though pharmacokinetically limited therapeutic effects and that use of lipid nanotechnology (SNEDDS, NLC, and nanoemulgel) to these same phytoconstituent combinations is a pharmacologically sound approach to greater and more predictable therapeutic efficacy.[46]

REGULATORY LANDSCAPE, STANDARDIZATION CHALLENGES, AND THE PATH TO CLINICAL TRANSLATION

The regulatory landscape for nano-modified Ayurvedic lipid formulations is a real challenge as it falls in the area between two regulatory categories for which there is no clear demarcation till now. Classical ayurvedic formulations, such as ghrita and taila, are regulated in India under the Drugs and Cosmetics Act 1940, and are under the regulatory purview of both the Ministry of AYUSH (which regulates around 8,000 organised ayurvedic medicines) and the Central Drugs Standard Control Organisation (CDSCO). A modified or nano-reformulated classical ghrita however no longer fits into the classical category of AYUSH, as it includes synthetic excipients (Cremophor EL, Tween 80, Transcutol P) and is prepared through modern pharmaceutical methods that are not as per Sneha Paka methodology mentioned in the Ayurvedic Formulary of India.[47] Concurrently, it may not be considered as a phytopharmaceutical according to the definition as per the Notification No: GSR 918(E) of the CDSCO Gazette 2015 that stipulates that phytopharmaceutical should be purified and standardized fractions of bioactive phytochemicals from a single plant extract a condition that is not met in the case of the ghrita made using a multi-plant herbal mixture and ghee. The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA), which was set up under Directive 2004/24/EC, offers a simplified procedure to register traditional herbal medicinal products in the EU member states, which are based on the demonstration of historical use and safety but do not require efficacy data of the quality required for new chemical entities. If the traditional herbal preparation is reformulated as a nanoformulation, however, then the product is not eligible for the benefit of traditional use documentation for the nano-engineered form and is re-introduced to the full EMA/FDA

evaluation pathway.[47] The FDA's Botanical Drug Guidance for Industry and EMA's nanomedicine guidelines necessitate the physicochemical characterization parameters such as particle size distribution, chemical composition, drug loading and release kinetics which are absent from classical Ayurvedic pharmacopoeial testing. This leaves a regulatory gap – traditional characterization standards apply to the classical preparation, but modern standards to the nanoformulation, which is not the same. A feasible way forward is to approach the quality problem in a way that can be envisioned as a dual-standard framework. The quality of classical ghrita base should be determined by satisfying the relevant parameters of Ayurvedic Pharmacopoeia of India (API) and Ayurvedic Formulary of India (AFI) parameters namely acid value, saponification value, iodine value, refractive index, specific gravity, moisture and HPTLC fingerprint against the reference standards, which ensures that the lipid base maintains the pharmaceutical attributes of the conventional ghrita preparation.[48] The standard characterization suite of SNEDDS / NLC (droplet size, PDI, zeta potential, encapsulation efficiency, in vitro drug release and thermodynamic stability) should be performed independently, and should be validated against modern pharmaceutical characterization requirements for the nanoformulation layer. These together constitute a twin quality profile, which defines the product clearly in the context of the Ayurvedic tradition from which it comes and the modern pharmaceutical context in which it is attempting to get regulatory recognition. The available clinical evidence is weak: some of the preparations (e.g. Brahmi Ghrita and Guggulu Tiktaka Ghrita) have reasonably well documented pre-clinical evidence, while there are few or none large-scale, well-designed RCTs with pharmacokinetic evidence for their nano-modernized variants. This is not only a regulatory hurdle, but the single most important hurdle that mainstream pharmaceuticals must overcome for the Ayurvedic modernization process outlined in this review to gain acceptance.[49]

FUTURE PERSPECTIVES

Based on the evidence presented in this review, the scientific pathway for the modernization of Ayurvedic lipid formulation points towards three future research directions that logically follow from the current evidence and each have a different level of scientific maturity, with each potentially significantly advancing the translational timeline. The first and most imminent direction is solid-SNEDDS platforms for the oral ghrita based preparations.[50] Although liquid SNEDDS have the potential to be therapeutic, they have their own inherent physical stability challenges: segregation of components, leakage from capsule dosage forms, and potential for oxidative degradation, especially when combined with the complex

phytochemical composition of many herbal payloads and varying moisture sensitivity of their components. Thermodynamic stability of the liquid SNEDDS can be achieved by solidifying them to dry nanoemulsion powder preconcentrate forms on the surface of mesoporous carriers (e.g., Neusilin, magnesium alumino-metasilicate) or polymer-coated porous silica with surface area of approximately 300 m^2/g, oil adsorption capacity of 2.7–3.4 mL/g), improved patient compliance, and the potential to process them into tablets or capsules with standard pharmaceutical equipment.[51] It has been recently shown that the spray drying and adsorption methods generally maintain the nanoemulsification performance of the pre-solidified liquid system, and that solid forms made by these methods can give bioavailability results similar or better than the liquid SNEDDS. With applied solid-state conversion, formal pharmacokinetic validation would be possible, in vitro-in vivo correlation (IVIVC) data could be generated, and finally, regulatory submission could be made, all of which are missing steps in the current evidence base – both as a Brahmi Ghrita SNEDDS and as a Guggulu Ghrita lipid nanocarrier. The second direction is the "omics-guided standardization". Modernization of these preparations requires the use of one or two marker compounds arbitrarily chosen to define the CQA and these compounds are not suitable for the multi-target pharmacology of ghritas.[52] If metabolomics-based fingerprinting was used to obtain untargeted LC-MS/MS-based comprehensive phytochemical profile at each stage of Paka, these clusters of markers will have a scientifically defensible basis in correlation with the pharmacological activity rather than analytical convenience alone. This method, which has been used in published literature for conventional formulations using polyherbs, would enable the CQA definition problem to be resolved from an arbitrary compromise to a data driven pharmaceutical decision more applicable to the modernized formulation of nanocrystals in order to preserve the therapeutic phytochemical signature of the classical formulation in all batches. The third is the computational formulation design. Molecular dynamics simulations and conductor-like screening model for real solvents (COSMO-RS) based solubility predictions are well-established computational tools in the modern SNEDDS development that can predict the drug-excipient interaction energy, drug solubility in candidate lipid excipients, and the emulsification behavior from the molecular structure data alone. Such computational approaches could be used in the context of structural diversity for the various phytoconstituents (limonoids, triterpenoids, steroidal lactones, alkaloids, phenolics) found in Ayurvedic ghritas, and allow for rational identification of the most likely combinations of lipid excipients to co-solubilize the complete phytochemical profile of a specified ghrita preparation, significantly reducing the pre-formulation screening cycle time,

which is the longest when using complex botanical payloads.[53] Several weighty conclusions can be drawn from the evidence reviewed in this article: Ayurvedic lipid preparations are not scientific anachronisms. They are empirically optimized lipid-based drug delivery systems, in which millennia years of clinical experience have guided towards formulation decisions (lipid base selection, thermal processing parameters, multi-botanical active ingredient combinations, and route specific Paka stage endpoint criteria) that follow closely the rules of contemporary pharmaceutical LBDDS design. They represent a critical shortcoming in the technology rather than in theory; they were designed without the excipient science, analytical instruments, or understanding of the mechanisms required to progress from a point where they are merely adequate to a point where they can be optimized for pharmaceutical use. Nanotechnology based modernization offers just those tools. It is now possible to take these ancient, but pharmacologically well-informed preparations and design them rationally for pharmaceutical purposes and to do so is a very good reason to speed up this process, since there is a huge population of patients for whom these preparations have been clinically valuable.[54]

CONCLUSION

The data presented in this article strongly suggests that the formulation of ayurvedic ghrita and taila preparations is not a primitive dosage form awaiting the replacement of modern formulations, but an empirical optimization of lipid based delivery systems whose formulation concepts, in terms of selection of the lipid base, processing conditions, combinations of several phytoconstituents, and endpoint criteria, span several centuries ahead of the principles of modern self-emulsifying and lipid nanocarrier science. Conceptual analogies are not sufficient to prove the convergence; it has to be directly proven by the analysis: The fatty acid profile of cow ghee is altered during the Murchana pre-treatment, similarly as in the HLB optimization for modern SNEDDS; the polar active botanical ingredients of classical ghrita are demonstrated to be present in submicron colloidal form within the lipid matrix, which is the same as is required for successful lipid phase drug loading in modern SNEDDS; the mass transfer mechanism of Paka processing is shown to be analogous to the thermodynamic driving force for lipid phase drug loading used in modern SNEDDS. The difference between a classical ghrita and a pharmaceutically validated SNEDDS is not that they might contain different drugs, but that they are engineered in terms of excipient composition, controlled nanodroplet size, and reproducible pharmacokinetic profile that can only be achieved using modern formulation technologies. The field has

reached a productive intersection whereby computational solubility prediction, metabolomics-based standardization of traditional preparations, and solid-state conversion technologies can all act together to enable the transformation of an empirically competent traditional preparation into a rigorously characterized, clinically validated nanomedicine, and the therapeutic population that has depended on these traditional preparations for millennia deserves the full benefit of that transformation.

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