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Pharmaceutico-Analytical Study of *Muktashukti Pishti* and *Muktashukti bhasma* and Comparative Evaluation of their Relative Oral Bioavailability

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Authors' contributions

This work was carried out in collaboration between all authors. Author SK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AW managed the analyses of the study. Authors BR and DR managed the literature searches. All authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: *Shukti* (Oyster) is a very commonly occurring calcium form. It is rich source of calcium & minerals. As per text it can be converted into two forms which are *bhasma* (calcinated ash) and *pishti* (powdered form without *agni*).These forms may have different rate of absorption. This needs to be studied.
Aim: To study Pharmaceutico-analytical study of *Muktashukti pishti & Muktashukti bhasma* and comparative evaluation of their relative oral bioavailability.
Materials and methods: The two formulations will be prepared from *shukti* (oyster). By triturating with *Gulabjala Muktashukti pishti* will be prepared and by traditional *puta* method *Muktashukti bhasma* will be prepared. The prepared formulations will be assessed for *Bhasma Pariksha* mentioned in *Ayurveda*. Organoleptic characters, physicochemical parameters and Particle size distribution analysis, SEM-EDX (Scanning Electron Microscopy, Energy Dispersive X-Ray Analysis), FTIR (Fourier-transform infrared spectroscopy), XRD (X-Ray Diffraction), GCMS (Gas

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Chromatography Mass Spectrometry) will be evaluated. To assess the relative oral bioavailability of *Muktashukti pishti* & *Muktashukti bhasma* study will be conducted in healthy volunteers and will be compared with the standard calcium supplement. The study will be conducted in between two test groups and standard group.

Observation and results: The analytical parameters will be assessed and compared in *Muktashukti bhasma* and *Muktashukti pishti*. For relative oral bioavailability Blood serum calcium will be assessed in all three groups. By applying unpaired "t" Test, One-way ANOVA the statistical significance can be measured.

Conclusion: The pharmaceutical & analytical study of *Muktashukti pishti and Muktashukti bhasma* will provide the standard parameters and clinical comparative evaluation with standard will generate evidence for better bioavailability.

Keywords: Muktashukti pishti; muktashukti bhasma, analysis; bioavailability.

1. INTRODUCTION

Rasashastra & *Bhaishajya Kalpana* is one among the branches of *Ayurveda*, which deals with Ayurvedic pharmaceutics. *Rasashastra* deals with pharmaceutical preparation of *Ayurveda* related to metallic origin [1]. Most emphasis is given with respect to the therapeutic uses of mercurial, mineral and metallic medicines including calcium containing formulations specified for various disease conditions [2]. *Bhasma* is a metallic or mineral preparation treated with specific liquid which are mostly juice, decoction or urine of animals & then exposed to quantum of heat according to their suitable properties known as *puta*. It is an ash obtained through incineration. The raw material undergoes an elaborate process of purification (*shodhan*) followed by *maran*. The end product i.e. *bhasma* is expected to be a non-toxic material which can be readily absorbed & assimilated.

Pishti is a fine powder of medicine that absorbs in body easily and possess similar efficacy like that of *bhasma*. The same purified drug can be used for making *pishti* as used for making *bhasma* but there is difference in preparation method and their potency. *Pishti* also has quick absorption and assimilation because of micro-fine particles like *bhasma* [3]. Use of metallic & mineral preparations for maintaining health &curing diseases is a unique feature of *rasa shashtra*. *Sudhavarga dravya* are grouping of drugs that possess high calcium content. It includes *Shankha, Shukti, Pravala, Godanti, Dugdhapashan, Samudraphena, and Mrudgarshrunga* [4].

Calcium is a trace element that every living organism need. It is the most essentialnutrient in the human body [5]. Human needs calcium to building & maintaining strong bones & 99% of the body calcium is present in the bones & teeth. It is also useful for maintaining healthy communication between the brain & body parts. It has very essential role in physiological function of regulation of gastro intestinal secretions, muscular movement, bone structure and cardiac physiology [6].

Shukti is a readily available & most cost-effective drug from *sudhavarga. Muktashukti* and *jalashukti* are the two types of *shukti*. *Muktashukti* is the outer hard covering shell of *mukta*. This provides *mukta* protection, nutrition and structural frame for its survival and hence called by synonyms *muktagriha, muktamata and muktamandira*. The *shukti* which not contain *mukta* or Mollusa into it and which is obtained from sea is called as *jalashukti*. Shukti is an source of various elements like zinc, iron, calcium, selenium as well as vitamin A and vitamin B12; dietary supplements may contain calcium carbonate from it [7]. "*Shuktija yoga*" is mention in *visarpachikitsa* externally for *pradeha* [8]. It is used in *netraroga* for *anjana karma* [9]. *Shukti* in many formulations cures diseases like *shoola, amlapitta, grahani* etc [10]. *Ayurved prakash* explain *shukti* in the preparation of "*kshara bandha"* [11]. *Muktashukti bhasma* is having cooling effect. It is useful in Heart disease and giving strength to brain it is useful in *pittaj vyadhi,* fever & flatulence [12]. *Muktashukti pishti* reduce excess *pitta* and heat due to its *sheeta virya*. It is beneficial in heart burn, abdominal pain, anorexia, calcium deficiency etc.

The analytical study & the therapeutic efficacy of the drug is already mentioned and established with research studies but, the *Muktashukti pishti* & *Muktashukti bhasma* may differ in the analytical parameters. However, same material undergoes different pharmaceutical methods to obtain different end product, may shows

difference in bioavailability & thus therapeutic efficacy also. Considering this the study has been planned to assess the relative oral bioavailability of *Muktashukti pishti* & *Muktashukti bhasma* along with standard calcium supplement.

For all life stages Calcium is very essential compound. *Sudhavargadravya* possess high calcium content. Out of which *Shukti* is easily available & cheap source. Pharmaceutico-analytical study of the *Muktashukti pishti* & *Muktashukti bhasma* was performed in previous works but the bioavailability study of these both formulations was not done. However, their therapeutic efficacy may vary as per method of preparation. Considering this, the study is planned with development of standard operating process and for their relative oral bioavailability with standards. The drug given through oral route appears in some quantity only, in the blood plasma [13]. In this study the plasma concentration will be assessed in all three groups. Out of these herbo-mineral calcium supplements, one which shows significant bioavailability with that of standard calcium supplement, can be used safely without giving any side effects as standard calcium supplement shows side effects like constipation & abdominal discomfort.

2. MATERIALS AND METHODS

Study design: Randomized single blind controlled study

Sample size: The sample size calculation for a bioavailability and bioequivalent study is dependent on multiple factors like power, intra subject coefficient of variation, expected geometric mean ratio.

According to C. Bhupati and V.H. Vajjha. (STATISTICA, anno LXXVII, n.1, 2017), power of 85% would be reasonable for bioavailability study to conduct on healthy volunteers. By considering the values of Lower Bound (LL) =0.80, Upper bound (UL) = 1.25, Alpha=0.05, Geo Mean Ratio (GMR) = 0.947, Coefficient of Variation (CV) = 0.239 as fixed, the sample size can be calculated as below.

Pharmaceutical study: pharmaceutical preparation of *Muktashukti bhasma & Muktashukti pishti* will be prepared. It will be done by following steps.

I) Procurement and Authentication of Raw materials:

1. *Shukti* will be procured from Shri Shaila Agency, Nagpur and will be authenticated by the Department of *Rasashashtra* (MGACH & RC).
2. *Kumari* & *Gulabpushpa* will be collected from medicinal plants garden (MGACH & RC), and primarily Authenticated by *Dravyaguna* Department.
3. *Kanji* & *Gulabjal* will be prepared in Dattatraya Rasashala which is required for *Shodhan* of *Mukta shukti* & preparation of *Muktashukti pishti* respectively.

II) *Shodhana* (purification) of *Shukti: [14]*

Small pieces of *shukti* will be made with the help of mortar & pestle

⇩

These pieces will tied in a clean cloth to make a *pottali*

⇩

The *potalli* will be subjected to *swedan* in vessel containing *kanji* for 3 hrs (*1 yam*)

⇩

After it *shukti* pieces will be washed with warm water & dried.

III) *Preparation of Muktashukti pishti [15]*

Shodhita muktashukti will be pounded in *khalva yantra*

⇩

Triturating will be done in *khalva yantra* till 21 days by adding *Gulabjala* into it.

IV) Marana* (incineration) of *Shukti: [16]

Shodhit shukti pieces will be crushed again in a *khalvayantra*

⇩

Kumari swarasa will be added into it to make a paste

⇩

Chakrika will be made from it & allowing to dry

⇩

Prepared *chakrika* will be kept in *sarava*

⇩

Sandhi lepan will be done and allowing to dry the *sarava*

⇩

Then it will be subjected to heating for giving one *gajaputa* till *sidhi pariksha* attains.

Analytical study: For analytical study organoleptic characters and physicochemical parameters and other sophisticated tests like Particle size distribution analysis, SEM –EDX, FTIR, XRD, and GCMS will be done [17].

Study Parameters [18]

Analytical study: Under analytical study the organoleptic study will be performed under following heads by using the sense organs

- **Specifications** –

a. Colour
b. Odour
c. Taste
d. Touch

- **Physico-Chemical analysis**

1. pH(10% aqueous extract)
2. Loss on drying at 105^0 C
3. Ash value analysis under this , Total ash value , Water soluble ash and Acid-insoluble ash will be analysed
4. Water soluble extractive values and alcohol soluble extractive values will be calculated

Sophisticated Instrumental analysis

1. Particle size distribution analysis
2. SEM –EDX
3. FTIR
4. XRD
5. GCMS

Bioavailability study: It will be randomized single blinded study in which 30 healthy Volunteers in each group will be selected (total 90 volunteers) from *Swastharakshan* OPD, Mahatma Gandhi *Ayurvedic* College Hospital and Research Centre, salod (H), Wardha.

Eligibility criteria: Age group from 20 to 40 years of volunteers will be taken in the study. The screening parameters for this will be physical examination and complete blood count (CBC), blood sugar, liver function test, Kidney function test, lipid profile, blood pressure. The volunteers with normal values will be selected for the study.

Interventions: In total 90 volunteers one group with 30 volunteers will be standard group in which standard Calcium supplement were given 500mg once a day before meal, second group with 30 volunteers *Muktashukti pishti* will be given 500mg once a day before meal and the third group with 30 volunteers *Muktashukti bhasma* will be given 500mg once a day before meal. The study will be conducted for 15 days.

Investigation during treatment: Complete blood count, Liver Function test, Kidney Function test, Lipid profile, Blood sugar, Urine routine and microscopic, Blood Serum Calcium level will be done for screening.

Criteria for discontinuing or modifying allocated interventions: If patient having any problem related to consumption of medicine or having any sensitivity will be withdraw from study.

Follow up period after treatment: After 24 hours, 3^{rd} day, 7^{th} day, 15^{th} day of drug administration.

Implementation: Principal invigilator will allocate and enroll the patient.

Observation & Results: The pharmaceutically prepared *Muktashukti pishti and Muktashukti bhasma* will be analyzed for organoleptic parameters and physichochemical parameters. The parameters will be compared. The sophisticated instrumental analysis, SEM –EDX, FTIR, XRD and GCMS of *Muktashukti pishti and Muktashukti bhasma* will be done and compared as per the results obtained.

Table 1. The sample size and power

The sample size and power								
Sample	54	50	47	44	35	30	26	24
Power	97.9	97.0	96.0	95.0	90.0	85.0	80.0	76.6

Table 2. Dose and frequency

Sr no	Group	Sample size	Intervention	Dose & frequency	*Anupan*(Vehicle)	Duration
1.	Standard group	30 volunteers	Standard calcium compound (SDC)	500mg (OD) before meal	Water	15 days
2.	Test group 1	30 volunteers	*Muktashukti pishti* (MSP)	500mg (OD) before meal	Water	15 days
3.	Test group 2	30 volunteers	*Muktashukti bhasma* (MSB)	500mg (OD) before meal	Water	15 days

Table 3. Blood collection after administration of drug

Group	Blood collection after administration of drug				
SDC	00	24 hrs	3rd day	7thday	15thday
MSP	00	24 hrs	3rd day	7thday	15thday
MSB	00	24 hrs	3rd day	7thday	15thday

Table 4. Coding of blood sample of Group SDC

Group SDC(n=30)	Blood collection after administration of drug				
	00	24hrs	3rd day	7th day	15th day
SDC1	SDC1-00	SDC1-24	SDC1-3	SDC1-7	SDC1-15
SDC2	SDC2-00	SDC2-24	SDC2-3	SDC2-7	SDC2-15
SDC3	SDC3-00	SDC3-24	SDC3-3	SDC3-7	SDC3-15
SDC4	SDC4-00	SDC4-24	SDC4-3	SDC4-7	SDC4-15
SDC5	SDC5-00	SDC5-24	SDC5-3	SDC5-7	SDC5-15
SDC6	SDC6-00	SDC6-24	SDC6-3	SDC6-7	SDC6-15
SDC7	SDC7-00	SDC7-24	SDC7-3	SDC7-7	SDC7-15
SDC8	SDC8-00	SDC8-24	SDC8-3	SDC8-7	SDC8-15
SDC9	SDC9-00	SDC9-24	SDC9-3	SDC9-7	SDC9-15
SDC10	SDC10-00	SDC10-24	SDC10-3	SDC10-7	SDC10-15
SDC11	SDC11-00	SDC11-24	SDC11-3	SDC11-7	SDC11-15
SDC12	SDC12-00	SDC12-24	SDC12-3	SDC12-7	SDC12-15
SDC13	SDC13-00	SDC13-24	SDC13-3	SDC13-7	SDC13-15
SDC14	SDC14-00	SDC14-24	SDC14-3	SDC14-7	SDC14-15
SDC15	SDC15-00	SDC15-24	SDC15-3	SDC15-7	SDC15-15
SDC16	SDC16-00	SDC16-24	SDC16-3	SDC16-7	SDC16-15
SDC17	SDC17-00	SDC17-24	SDC17-3	SDC17-7	SDC17-15
SDC18	SDC18-00	SDC18-24	SDC18-3	SDC18-7	SDC18-15
SDC19	SDC19-00	SDC19-24	SDC19-3	SDC19-7	SDC19-15
SDC20	SDC20-00	SDC20-24	SDC20-3	SDC20-7	SDC20-15
SDC21	SDC21-00	SDC21-24	SDC21-3	SDC21-7	SDC21-15
SDC22	SDC22-00	SDC22-24	SDC22-3	SDC22-7	SDC22-15
SDC23	SDC23-00	SDC23-24	SDC23-3	SDC23-7	SDC23-15
SDC24	SDC24-00	SDC24-24	SDC24-3	SDC24-7	SDC24-15
SDC25	SDC25-00	SDC25-24	SDC25-3	SDC25-7	SDC25-15
SDC26	SDC26-00	SDC26-24	SDC26-3	SDC26-7	SDC26-15
SDC27	SDC27-00	SDC27-24	SDC27-3	SDC27-7	SDC27-15
SDC28	SDC28-00	SDC28-24	SDC28-3	SDC28-7	SDC28-15
SDC29	SDC29-00	SDC29-24	SDC29-3	SDC29-7	SDC29-15
SDC30	SDC30-00	SDC30-24	SDC30-3	SDC30-7	SDC30-15

The relative oral bioavailability of *Muktashukti pishti and Muktashukti bhasma* in comparison with standard calcium will be observed.

Statistical analysis: Statistical analysis will be done by applying unpaired't' Test & One-way ANOVA. Unpaired t test will be applied for pre and post assessment of Blood serum calcium. One way ANOVA will be applied for assessment of statistical significance related to Blood serum calcium, in between three groups.

3. DISCUSSION

Ayurveda formulations are becoming popular throughout the world. Rising population, cost effectiveness, less side effects, available at all places are few remarkable causes regarding the use of herbal and mineral drugs as a source of medicines and health supplements [19]. With growing importance, its safety and efficacy studies must be conducted for global acceptance [20].By incineration the bioavailability may be increased and the drug action may be potentiated. [21] The analysis of MSB and MSP will be compared. In both the samples organoleptic characters that is color, odor, taste will be assessed. Particle size will be assessed, which is a major parameter by means of which rate of absorption can be assessed in MSB and MSP. From scanning Electron Microscopy Energy Dispersive X-Ray Analyzer (SEM EDX) is elemental identification along with quantitative composition can be finding out in MSB and MSP [22]. By Fourier Transform Infrared Spectroscopy (FTIR) chemical bonds will be identified in MSP and MSB [23]. With the help of X-Ray Diffraction (XRD) the crystalline structures of the molecule will be recognized in both the samples that are MSP and MSB [24]. GC-MS technique will be used to analyze complex organic and biochemical mixtures between MSP and MSB [25]. Related studies of standardization of few ayurvedic drugs were reported [26,27].Pharmaceutico-analytical studies and reviews by Khatib et. al. were reviewed [28,29].The relative oral bioavailability between MSP & MSB and standard calcium will be assessed. The Herbo mineral formulations are the most efficacious formulations [30]. However, the assessment will be done by evaluation of serum calcium in all of the three groups. The plasma concentration of the serum calcium will be plotted against time in all the three groups. It is represented by the curve, known as area under curve [31].

Table 5. Coding of blood sample of group MSP

Group MSP(n=30)	Blood collection after administration of drug				
	00	24hrs	3rd day	7th day	15th day
MSP1	MSP1-00	MSP1-24	MSP1-3	MSP1-7	MSP1-15
MSP2	MSP2-00	MSP2-24	MSP2-3	MSP2-7	MSP2-15
MSP3	MSP3-00	MSP3-24	MSP3-3	MSP3-7	MSP3-15
MSP4	MSP4-00	MSP4-24	MSP4-3	MSP4-7	MSP4-15
MSP5	MSP5-00	MSP5-24	MSP5-3	MSP5-7	MSP5-15
MSP6	MSP6-00	MSP6-24	MSP6-3	MSP6-7	MSP6-15
MSP7	MSP7-00	MSP7-24	MSP7-3	MSP7-7	MSP7-15
MSP8	MSP8-00	MSP8-24	MSP8-3	MSP8-7	MSP8-15
MSP9	MSP9-00	MSP9-24	MSP9-3	MSP9-7	MSP9-15
MSP10	MSP10-00	MSP10-24	MSP10-3	MSP10-7	MSP10-15
MSP11	MSP11-00	MSP11-24	MSP11-3	MSP11-7	MSP11-15
MSP12	MSP12-00	MSP12-24	MSP12-3	MSP12-7	MSP12-15
MSP13	MSP13-00	MSP13-24	MSP13-3	MSP13-7	MSP13-15
MSP14	MSP14-00	MSP14-24	MSP14-3	MSP14-7	MSP14-15
MSP15	MSP15-00	MSP15-24	MSP15-3	MSP15-7	MSP15-15
MSP16	MSP16-00	MSP16-24	MSP16-3	MSP16-7	MSP16-15
MSP17	MSP17-00	MSP17-24	MSP17-3	MSP17-7	MSP17-15
MSP18	MSP18-00	MSP18-24	MSP18-3	MSP18-7	MSP18-15
MSP19	MSP19-00	MSP19-24	MSP19-3	MSP19-7	MSP19-15
MSP20	MSP20-00	MSP20-24	MSP20-3	MSP20-7	MSP20-15
MSP21	MSP21-00	MSP21-24	MSP21-3	MSP21-7	MSP21-15
MSP22	MSP22-00	MSP22-24	MSP22-3	MSP22-7	MSP22-15
MSP23	MSP23-00	MSP23-24	MSP23-3	MSP23-7	MSP23-15
MSP24	MSP24-00	MSP24-24	MSP24-3	MSP24-7	MSP24-15
MSP25	MSP25-00	MSP25-24	MSP25-3	MSP25-7	MSP25-15
MSP26	MSP26-00	MSP26-24	MSP26-3	MSP26-7	MSP26-15
MSP27	MSP27-00	MSP27-24	MSP27-3	MSP27-7	MSP27-15
MSP28	MSP28-00	MSP28-24	MSP28-3	MSP28-7	MSP28-15
MSP29	MSP29-00	MSP29-24	MSP29-3	MSP29-7	MSP29-15
MSP30	MSP30-00	MSP30-24	MSP30-3	MSP30-7	MSP30-15

Table 6. Coding of blood sample of group MSB

Group MSB(n=30)	Blood collection after administration of drug				
	00	24hrs	3rd day	7th day	15th day
MSB1	MSB1-00	MSB1-24	MSB1-3	MSB1-7	MSB1-15
MSB2	MSB2-00	MSB2-24	MSB2-3	MSB2-7	MSB2-15
MSB3	MSB3-00	MSB3-24	MSB3-3	MSB3-7	MSB3-15
MSB4	MSB4-00	MSB4-24	MSB4-3	MSB4-7	MSB4-15
MSB5	MSB5-00	MSB5-24	MSB5-3	MSB5-7	MSB5-15
MSB6	MSB6-00	MSB6-24	MSB6-3	MSB6-7	MSB6-15
MSB7	MSB7-00	MSB7-24	MSB7-3	MSB7-7	MSB7-15
MSB8	MSB8-00	MSB8-24	MSB8-3	MSB8-7	MSB8-15
MSB9	MSB9-00	MSB9-24	MSB9-3	MSB9-7	MSB9-15
MSB10	MSB10-00	MSB10-24	MSB10-3	MSB10-7	MSB10-15
MSB11	MSB11-00	MSB11-24	MSB11-3	MSB11-7	MSB11-15
MSB12	MSB12-00	MSB12-24	MSB12-3	MSB12-7	MSB12-15
MSB13	MSB13-00	MSB13-24	MSB13-3	MSB13-7	MSB13-15
MSB14	MSB14-00	MSB14-24	MSB14-3	MSB14-7	MSB14-15
MSB15	MSB15-00	MSB15-24	MSB15-3	MSB15-7	MSB15-15
MSB16	MSB16-00	MSB16-24	MSB16-3	MSB16-7	MSB16-15
MSB17	MSB17-00	MSB17-24	MSB17-3	MSB17-7	MSB17-15
MSB18	MSB18-00	MSB18-24	MSB18-3	MSB18-7	MSB18-15
MSB19	MSB19-00	MSB19-24	MSB19-3	MSB19-7	MSB19-15
MSB20	MSB20-00	MSB20-24	MSB20-3	MSB20-7	MSB20-15
MSB21	MSB21-00	MSB21-24	MSB21-3	MSB21-7	MSB21-15
MSB22	MSB22-00	MSB22-24	MSB22-3	MSB22-7	MSB22-15
MSB23	MSB23-00	MSB23-24	MSB23-3	MSB23-7	MSB23-15
MSB24	MSB24-00	MSB24-24	MSB24-3	MSB24-7	MSB24-15
MSB25	MSB25-00	MSB25-24	MSB25-3	MSB25-7	MSB25-15
MSB26	MSB26-00	MSB26-24	MSB26-3	MSB26-7	MSB26-15
MSB27	MSB27-00	MSB27-24	MSB27-3	MSB27-7	MSB27-15
MSB28	MSB28-00	MSB28-24	MSB28-3	MSB28-7	MSB28-15
MSB29	MSB29-00	MSB29-24	MSB29-3	MSB29-7	MSB29-15
MSB30	MSB30-00	MSB30-24	MSB30-3	MSB30-7	MSB30-15

4. CONCLUSION

The conclusion will be drawn from the results obtained and observations which will be observed. The conclusions will content analytical observations between MSB and MSP. For relative oral bioavailability the maximum concentration of calcium by plotting area under curve (AUC) will be assessed between standard calcium supplement tablet, MSP and MSB. According the blood plasma concentration of serum calcium, the graph will plotted against time in all three groups. The drug with maximum area under curve will be concluded as better relative oral bioavailable.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study will be conducted on human volunteers. The permission is obtained from the related institutional ethical committee (IEC).The approval reference number is Ref.No.MGACHRC/IEC/July-2020/64.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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