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STANDARDIZATION, FORMULATION DEVELOPMENT AND CHARACTERIZATION OF ANTIULCER DRUG: MUKTA BHASMA

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Keywords:

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ABSTRACT: Ayurveda is the holistic approach towards life, health, disease management through medicinal herbs minerals, diet and lifestyle leads to the great need for standardization of herbal medicine to maintain its safety and efficacy. Mukta bhasma is used in the treatment of bone metabolic disorders associated with calcium deficiency. It was prepared by Shodhana, Marana and Sharava samputa and the Standardization of bhasma are very necessary to confirm its identity and to determine its quality and purity. An attempt has been made to summarize the ancient and the advanced methods available for the standardization of bhasma. The dosage uniformity and patient compliance can be increased and adulteration can be decreased in ayurvedic powders by formulating them into tablets. The aim of the present work is to develop and evaluate Mukta Bhasma tablets using starch and acacia as a binder. The granules were prepared by the wet granulation method. The prepared tablets were evaluated for different parameters, acute toxicity of Mukta bhasma was conducted on albino rats. Mukta bhasma was administered orally in albino rats of single maximum limit dose 2000 mg/kg and general behavioral observation along with any mortality was recorded. Acute toxicity study shows that there is no adverse effect of bhasma on albino rats even at a single dose of 2000 mg/kg body weight that reveals that Mukta bhasma is safe in albino rats. The results suggest that this ayurvedic preparation cannot show any signs and symptoms of toxicity.

INTRODUCTION: Ayurveda is an ancient traditional medicine system, originated in India and evolved and practiced over thousands of years. Bhasma is the well-known potent preparation of the traditional Ayurveda. Bhasma literally means 'ash' which is obtained after incineration. Bhasma's are unique Ayurvedic metallic preparations with herbal juices/fruits or decoction, widely recommended for the treatment of a variety of chronic ailments.

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Bhasma's are biologically produced metallic nanoparticles obtained by calcination into ash and are taken along with milk, butter, honey, ghee, *etc*. [1, 2] this group of medicines can work even in smaller doses and may even control incurable diseases effectively.

In the present era, Ayurvedic physicians use medicines which are made from minerals, metals, animals as well as from vegetable products. Among these preparations products obtained from mineral metals, are supposed to be harmful to the human body. To avoid such side effects different Ayurvedic pharmaceutical processing techniques such as Shodhana, marana, *etc*. to convert metallic preparation into a nontoxic form of medicines are mentioned and also standardization of that

processes according to Ayurveda as well as modern analytical methods for standardization is also given in the Ayurveda texts. Standard is the numerical value that qualifies the parameters and thus determines the quality and purity of the material [3].

Mukta is a calcium compound categorized under the name "Sudha Vargiya Dravyas (calcium group drugs)" first named by Vaidya Yadavji Trikamji Acharya [4]. It is obtained from the Pearl shell or oyster found in the sea. Pearls (Mukta) are the calcareous concretions formed as protection against the irritation caused by foreign objects, either sand or minute parasites which have lodged inside the shell, between the mantle and the shell of the animal. A fold of soft tissue envelops the foreign particles and deposits layer after layer of nacre on it to form a pearl.

Nacre is composed of conchioline and calcium carbonate. Mukta (pearl) bearing qualities like Sheetavirya, Madhuravipaka, Kapha-pitta shamaka, Vrishya, Aaushyam, Balakara and Brihmana and also indicated in Kasa, Shwasa, Kshaya, Agnimandhya, Daha, Kaphaja Unmada, Vatavyadhi, Rajayakshma, Vishvikara and Netraroga [5].

MATERIALS AND METHODS: The raw material was procured from the local market (Maharashtra), India. The procurement of lemon from market time to time according to need is done. Nimbu Swaras is the fresh lemon juice obtained from the fruits of *Citrus lemon* (Family: Rutaceae). The lemon juice was filtered using muslin cloth [6].

Preparation of Mukta Bhasma: [6, 7]

a. Shodhana (Purification) of raw Mouktika.

b. Marana and Bhavana purified Mouktika.

Raw Mukta

Potalli containing Mukta

Dolayantra swedana in Nimbu Swarasa

Sharava samputa placed in Laghu puta

Igniting of Laghu puta

After 1st puta

After 2nd puta

Mukta bhasma

FIG. 1: PREPARATION OF MUKTA BHASMA

A. Shodhana (Method of Purification): About 270 gm of raw Mouktika was subjected to shodhana process. The outer side of Mukta shuktika was cleaned with a sharp knife to remove the impurities. Then it is broken into small pieces. It was wrapped with a cloth and pottali was prepared. Pottali was suspended with help of stick and immersed in Jambir swarasa. The Yantra was kept on fire for boiling. The boiling of Mouktika in Dolayantra was carried out for 3 h. The pottali was opened and mouktika was washed with hot water and kept for drying. 10 gm Shodhita mouktika was collected as a sample for analytical study.

B. Marana (Incineration) and Bhavana: The whole method of Moukti kamarana was completed in the following steps.

1. Bhavana (Trituration) with kumara swarasa.
2. Preparation of chakrikas (Pelletization).
3. Sharava samputa formation.
4. Laghuputa.

The lemon juice treated Mouktika was directly placed in silica crucibles which were subjected to heating in the muffle furnace for about 550 °C for 3 h. For this heating process *i.e.* Laghuputa, temperature was gradually increased to 550 °C in about 180 min. When the temperature reaches 550 °C, the temperature was maintained constant for about 3 h and after 3 h the temperature was decreased gradually to about 180 min to cool. After this process the Mouktika becomes brittle. These brittle Mouktika were collected and powdered with the help of mortar and pestle. The powdered mouktika is given Bhavana (trituration) with 40 ml of nimbu swarasa (lemon juice) for 3 h. Then Cakrikas (pellets) were prepared and dried. After drying these pellets were subjected to second puta for 800 °C. The process was repeated for the third time, 30 ml of nimbu swarasa was used and it was heated for 3 h. After cooling white colored Mouktika bhasma was obtained [6].

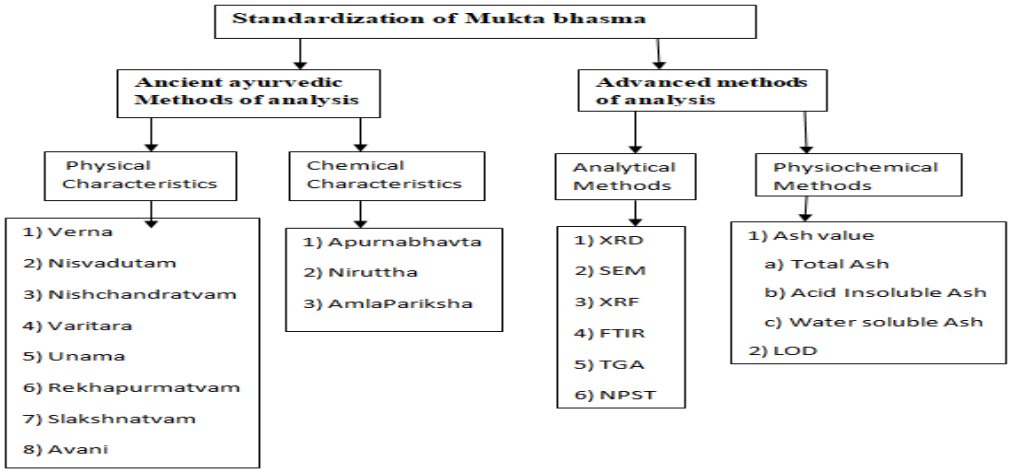
Observation during Mouktika Marana:

TABLE 1: OBSERVATION DURING MOUKTIKA MARANA

Test	Before Marana	Observation During Puta	
		I	II
Colour	Pale White	Milky white	Bright white
Taste	-	Slight Alkaline	Tasteless
Touch	-	Rough, Hard, Khara	Mrudu, Soft
Appearance		Powder	Very Fine Powder
Weight	250 gm	B.M 250 gm	B.M 200 gm
		A.M 210 gm	A.M 160 gm
Odor	-	Slight odor	Odorless
Varitaratva	-	70 - 80%	100%
RekhaPoornatva	-	NOB	OB
Loss	-	40 gm	40 gm

NOB- Not observed, B.M - Before Marana, OB - Observed, A.M- After Marana

Standardization of Mukta Bhasma:



Physical Characteristics:

Verna: A specific color is mentioned for each bhasma [8]. Bhasma is generally white, pale or red. Colour of preparation depends on parent material. Alteration in a specific color suggests that bhasma is not prepared properly.

Nisvadutam: A pinch of bhasma is placed on the tongue and its taste should perceive to be tasteless [9]. Bhasma prepared from metal may be an exception for this test.

Properly incinerated bhasmas should be of particular taste. It indicates the transformation of particular metallic taste to compounds of specific taste [8].

Nishchandratvam: Bhasma must be lustreless (Nishchandra) before therapeutic application. Luster is the character of metal which should not remain after proper incineration. For this test Bhasma is taken in a petri dish and is observed under bright sunlight, whether luster is present or not; if luster is present, it indicates further incineration [9].

Varitara: Bhasma should have lightness and fineness. This test is based upon the law of surface tension. Small amount of prepared bhasma is sprinkled over the cold and stagnant water in a beaker. Properly incinerated bhasma will float on water surface which states that prepared bhasma is light and fine.

Unama Test: It is further assessment of varitara test. A grain of rice is carefully placed on the floated layer of bhasma. Observe whether the grain floats or sinks. If the grain remains as it is on the layer, than bhasma can be considered as excellent [9].

Rekhapurnatvam: Bhasma particles should be of minimum size for easy absorption and assimilation in the body. When bhasma is spread between the thumb and index finger and rubbed, it should be so fine as to get easily into the lines and crevices of the fingers and should not be washed out from the lines of the fingers [10].

Slakshnatvam: It is the tactile sensation produced by bhasma by simple touch with fingertips. Tactile sensation can be properly absorbed and assimilated into the body without producing any irritation to the mucous membrane of gastrointestinal tract [8].

Avami: Bhasma should not produce nausea/ vomiting on administration [7].

TABLE 2: SHOWING PHYSICAL AND CHEMICAL CHARACTERISTICS ACCORDING TO ANCIENT AYURVEDIC METHODS

Parameter	Mukta bhasma
Verna	Dull white
Nisvadutam	Palatable
Nishchandratvam	Free from Luster
Varitara	Fine powder
Unama Test	Positive
Rekhapurnatvam	Positive
Slakshnatvam	Good

Physio-Chemical Methods: [11, 12]

Total Ash Value: It also helps in judging, identification of sample or purity of the drug. Mukta bhasma is evaluated for ash value and it was found 99.84% w/w.

Acid Insoluble Ash: Acid insoluble ash of Mukta bhasma was 0.34% w/w. The acid insoluble ash is a part of the total ash that is insoluble in dilute hydrochloric acid. This test for drug is therapeutically very important according to this test mukta bhasma is said to be good.

Water Soluble Ash: Mukta bhasma was estimated for water soluble ash was 8.31% w/w it denote that water is not a soluble media for it. The salivary secretions, gastric enzymes may play an important role in the efficacy of Mukta bhasma.

Loss on Drying at 110 °C: The moisture content of any pharmaceutical agent spoils not only the drug activity but also everything. Loss on drying at 110 °C is a physical test to detect the percentage of moisture content and hence the shelf life of the sample. Lesser the loss on drying at 110 °C better will be the drug. In the present study, Mukta bhasma was found to possess 0.24% w/w.

TABLE 3: SHOWING PHYSIOCHEMICAL METHODS ACCORDING TO ADVANCED METHOD OF ANALYSIS

Parameter	Mukta bhasma
Total ash w/w	99.84% w/w.
Acid insoluble ash w/w	0.34% w/w
Water-soluble ash w/w	8.31% w/w
Loss on drying	0.24% w/w

Analytical Methods: [13]

XRD Study: In XRD of Mukta bhasma, Peaks at d = 3.04 A0 (2θ = 29.3666) confirmed the presence of calcite as the major crystalline phase in sample and Bhasma contained calcite form of calcium carbonate ($CaCO_3$).

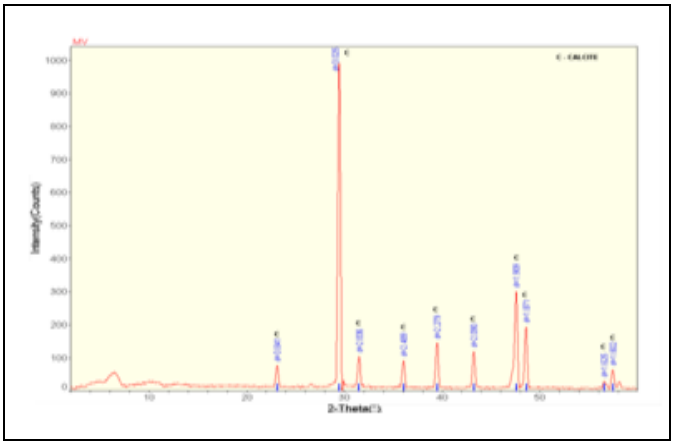


FIG. 2: XRD OF MUKTA BHASMA

X-Ray Fluorescence Spectrometer: X-Ray Fluorescence Analysis-one of the best Analytical techniques to perform elemental analysis in all kind of samples, no matter if liquids, solids or loose powders have to be analyzed. XRF combines highest accuracy and precision with simple and fast sample preparation for the analysis of elements from Beryllium (Be) to Uranium (U) in the concentration range from 100% down to the sub-ppm-level. The XRF spectrometer measures the individual component wavelengths of the fluorescent emission produced by a sample when irradiated with X-rays.

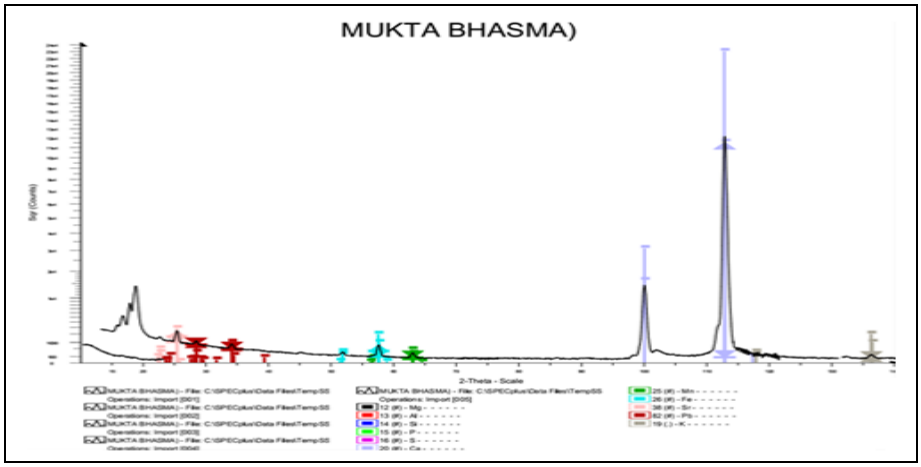


FIG. 3: XRF GRAPH OF MUKTA BHASMA

Scanning Electron Microscopy (SEM): The SEM photomicrograph of Mukta showed 20-100 nm particles in the sample. Particle size is one of the factors which will affect the dissolution and absorption of the drug. Particle size and surface area are inversely proportional to each other, as particle size decreases surface area increases. This leads to an increase in the dissolution of drugs and rapid absorption. Mukta is having a good dissolution rate and smaller particle size makes the drug in the bio-assimilable form so it is easily and readily absorb in the body and also SEM gave the information of chemical constituent so from observation it shows that Mukta bhasma having Calcium carbonate as main chemical constituents.

FTIR: This technique is based upon the simple fact that the substance shows marked selective absorption in the infrared region. After absorption of IR radiations, the molecules of the chemical substance vibrate at many rates of vibration, giving rise to close-packed absorption bands, called as IR absorption spectrum which may extend over a wide wavelength range. Various bands will be present in the IR spectrum which will correspond to the characteristic functional groups and bonds present in the chemical substance. It is used to establish the structure of an unknown compound and analysis of the functional group.

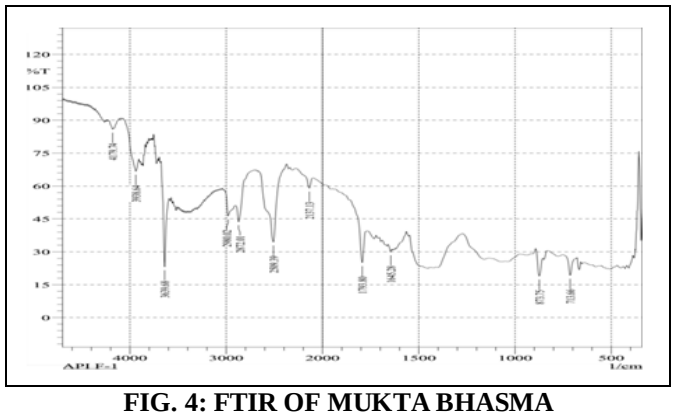
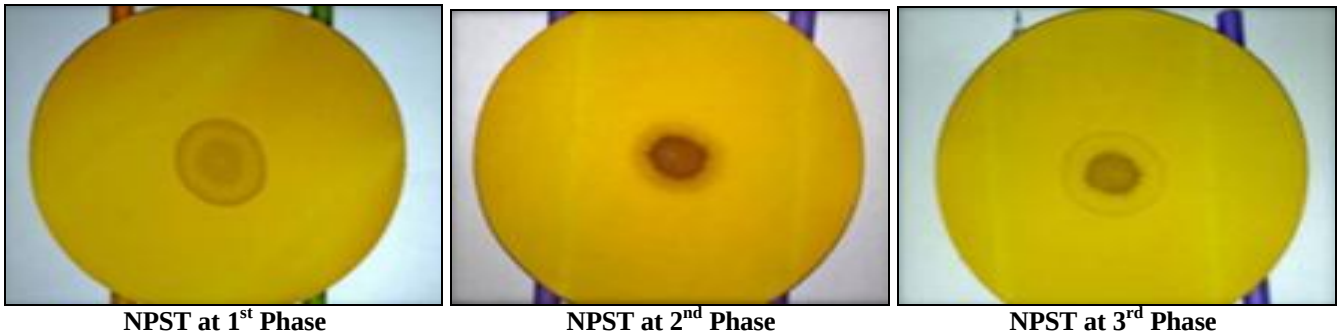


FIG. 4: FTIR OF MUKTA BHASMA

Namburi Phased Spot Test (NPST): [14, 15] The Mukta bhasma was subjected to NPST. Initially 0.25 g of bhasma was put into the test tube and heated on spirit lamp till the lower end of the test

tube becomes red hot. Heating was stopped once the charred smell starts to be emitted. The test tube was allowed to cool. Then 0.5 ml of distilled water was added to all the test tubes, shacked well and allowed to settle for 24 h. Then one drop of a clear solution of each sample was put on Haridra paper and observed for spot pattern in the following three phases:

- 1st phase: 0 to 5 min
- 2nd phase: 5 min to 20 min
- 3rd phase: 20 min to 1 day



NPST at 1st Phase NPST at 2nd Phase NPST at 3rd Phase

FIG. 5: DIFFERENT PHASES OF NPST

Acute Toxicity Study: [16, 17, 18] Acute toxicity tests are generally the first tests conducted. They provide data on the relative toxicity likely to arise from single drug exposure. The study was conducted after obtaining permission of Institutional Animal Ethical Committee and the CPCSEA registration number is 713/PO/Re/S/2002/CPCSEA. Rats fasted for 24 hrs before drug administration. A total of five animals were used. MSB uniformly dispersed in 2% *Gum acacia* suspension was administered as a single oral dose equivalent to 2000 mg/kg body weight. Food was withheld for a further 4 h.

Animals were observed individually at least once during the first 30 min after dosing, and then periodically during the first 24 h (with special attention during first 4 h), and daily thereafter for 14 days. Mortality, if any, was determined over a period of 2 weeks (OECD, 2001). LD_{50} was calculated as per OECD guidelines. Acute toxicity studies and dose determination The LD_{50} of Mukta Bhasma as per OECD guideline falls under class four with no signs of acute toxicity with up to a maximum dose of 2000 mg/kg. Any changes in normal behavioral pattern or signs and symptoms of toxicity and mortality were not observed up to this dose level.

Preparation of Standard Calibration Curve of Mukta Bhasma: Standard solution of Mukta Bhasma (100 µg/ml) was prepared by accurately weighing Mukta Bhasma (10 mg) and dissolving in 0.1 N hydrochloric acid and volume make up to 100 ml in the volumetric flask. Dilutions were made in the range of 5-25 µg/ml the absorbance values at 340 nm corresponding to each concentration were then evaluated and plotted taking absorbance on the Y-axis and concentration on the X-axis.

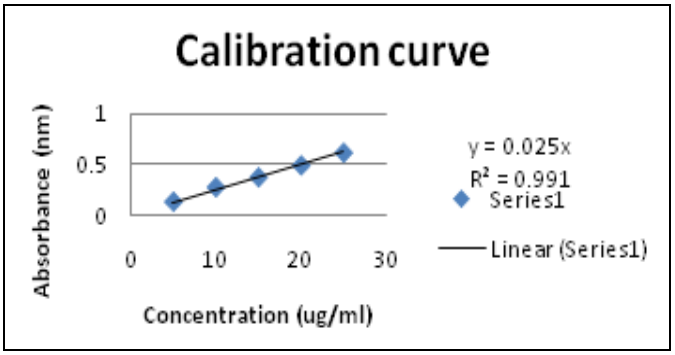


FIG. 6: CALIBRATION CURVE OF MUKTA BHASMA

TABLE 4: PRE-COMPRESSION PARAMETER OF ALL BATCHES

Batch	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.475 ± 0.1	0.534 ± 0.3	28.14 ± 0.12	13.12 ± 0.03	1.154 ± 0.02
F2	0.474 ± 0.2	0.543 ± 0.3	28.12 ± 0.13	14.1 ± 0.10	1.239 ± 0.03
F3	0.477 ± 0.2	0.532 ± 0.2	28.15 ± 0.11	13.9 ± 0.07	1.165 ± 0.02
F4	0.478 ± 0.1	0.535 ± 0.1	27.98 ± 0.09	13.14 ± 0.05	1.234 ± 0.04
F5	0.474 ± 0.2	0.539 ± 0.2	29.12 ± 0.014	14.34 ± 0.09	1.145 ± 0.06
F6	0.476 ± 0.1	0.534 ± 0.3	27.87 ± 0.12	14.32 ± 0.06	1.134 ± 0.02

Preparation of Mukta Bhasma Tablets: Mukta Bhasma was sifted through 40# sieve on a vibratory sifter and collected in a suitable container. Granules of Mukta Bhasma were prepared by the wet granulation method using acacia and starch as a binder. Granules were prepared manually on a laboratory scale using mortar pestle to form the wet mass with subsequent passing of the wet mass through 10 # sieve to get the uniform-sized granules. Granules were compressed into tablets of hardness 4 to 5 kg/sq.cm

TABLE 5: FORMULATION TABLE OF MUKTA BHASMA TABLETS

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Mukta bhasma	120	120	120	120	120	120
Starch	10	20	30	-	-	-
Acacia	-	-	-	10	20	30
Magnesium stearate	10	10	10	10	10	10
Talc	5	5	5	5	5	5
Lactose	55	45	35	55	45	35
Total	200	200	200	200	200	200

TABLE 6: EVALUATION OF POST-COMPRESSION PARAMETER

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	200.20 ± 0.01	3.5-4	2.5 ± 0.01	0.7 ± 0.041	98.01
F2	200.23 ± 0.03	3.5-4	2.6 ± 0.02	0.5 ± 0.039	99.36
F3	200.33 ± 0.05	4-5	2.5 ± 0.03	0.5 ± 0.078	97.21
F4	200.34 ± 0.02	3.5-4	2.5 ± 0.02	0.3 ± 0.02	99.67
F5	200.20 ± 0.04	4-4.5	2.6 ± 0.01	0.5 ± 0.06	99.24
F6	200.56 ± 0.02	4-4.5	2.5 ± 0.02	0.4 ± 0.08	99.38

***In-vitro* Dissolution Study:** The drug release study was carried out using ELECTROLAB dissolution testing apparatus II (paddle method) at 37 ± 0.5 °C and 50 rpm using 900 ml of 0.1 N HCl as a dissolution medium. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with a fresh dissolution medium. The samples were filtered through a membrane filter. The area was taken using Shimadzu UV 1800. The Mukta bhasma was detected at 340 nm in 0.1 N HCl. The percentage of drug release was calculated. Drug release data were kinetically evaluated and fitness of the release profiles to the kinetic models was investigated and the result shown in **Fig. 7** and **Table 7**.

Weight Variation: Weight variation test of the tablets was performed as per IP11. Twenty tablets of each formulation were weighed and the average weights and Maximum Deviation of average weights were calculated.

Dissolution Profile of all Batches of Mukta Bhasma Tablet:

TABLE 7: % DRUG RELEASE OF ALL BATCHES OF MUKTA BHASMA

Time	% Drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	24.12	21.23	36.21	28.60	29.94	15.23
2	38.12	58.21	39.12	30.12	61.75	36.21
3	75.23	57.23	49.25	45.63	80.48	48.59
4	78.14	68.23	51.89	58.78	83.48	55.2
5	80.12	71.21	67.89	66.12	85.36	68.24
6	82.69	75.26	77.23	71.23	90.41	71.12
7	87.14	78.96	78.54	75.47	92.25	74.23
8	89.26	85.14	82.36	78.25	95.19	77.65
9	91.55	85.32	88.47	88.10	95.96	81.41
10	92.36	86.14	90.21	89.56	96.14	85.36
11	93.58	87.45	92.12	93.47	97.40	87.98
12	94.21	90.30	93.89	94.24	97.89	90.38

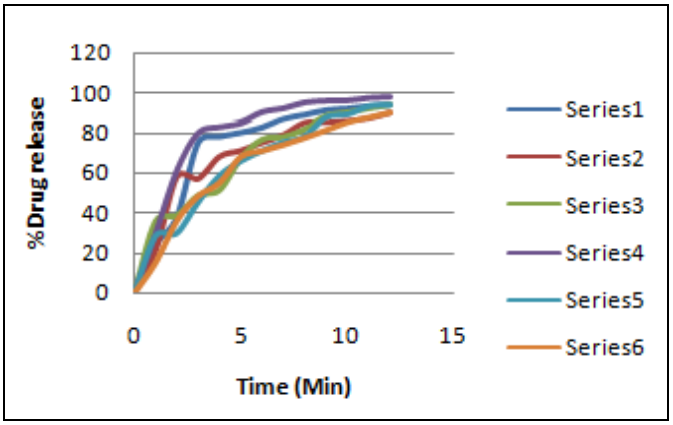


FIG. 7: % DRUG RELEASE OF ALL BATCHES

Accelerated Stability Studies: [19, 20] For the stability studies different tests were done. The appearance of the tablet remained clear and no significant variation in pH was observed after subjecting the formulations to stability stress for 21 days at 40 °C and 75% relative humidity and there was no significant change in drug content was observed after 21 days period it was shown in **Table 8**.

TABLE 8: OBSERVATION AFTER ACCELERATED STABILITY

S. no.	Time	Cum. % DR ± S.D. 1st Day	Cum. % DR ± S.D. 21st Day
0	0	0	0
1	10	29.94	24.12
2	20	61.75	38.12
3	30	80.48	75.23
4	40	83.48	78.14
5	50	85.36	80.12
6	60	90.41	82.69
7	70	92.25	87.14
8	80	95.19	89.26
9	90	95.96	91.55
10	100	96.14	92.36
11	110	97.40	93.58
12	120	97.89	94.21

CONCLUSION: Mukta is one of the aquamarine gems which is a rich source of calcium and used in medical practice since ancient times. To get quality of Mukta bhasma two Laghu- putas are required during the preparation of Mukta bhasma the yield was 160 gm and weight loss was 80 gm during the process Marana. There is a need for standardization by the ancient method and some analytical methods were performed and ensure the quality of prepared Mukta bhasma. The mean particle size of Mukta bhasma is 20-100 nm observed by SEM and also it gave the information of chemical constituent so from observation it shows that Mukta bhasma having Calcium carbonate as main chemical constituents. XRD study of Pearl powder was found in the form of Aragonite $CaCO_3$ and Mukta Bhasma was in Calcite $CaCO_3$ form. XRF analysis revealed that the sample contains Ca as a major element, Mg, Si,P, Mn, Sr as minor elements.

Mukta bhasma was selected for the management of peptic ulcer and for patient compatibility and dose accuracy table was formulated and its Preformulation study was performed after observation we conclude that powder was not having sufficient flow property so we have to prepare a granule of that. Then we selected excipients that are needed for the formulation of tablet and firstly compatibility study was performed by FTIR and from that, we conclude that all excipients that are used in formulation are compatible before tablet compression granules were evaluated for angle of repose, Bulk density, Tapped density, Hausner's ratio, Carr's index *etc*. After compression tablet were subjected to post compressional evaluation that is weight variation, Thickness, Hardness, % Friability, Disintegration test, Dissolution test and drug content was also found in the range of 90-110%. The percentage of *in-vitro* drug releases for F5 was observed to be within the limit that is 97.89. The drug release of F1, F2 and F3 after 2 h 94.21, 90.30% and 93.89% respectively, the drug release of batch F4 and F6 was 94.24% and 90.38%. Then performing acute toxicity study, this study concludes LD_{50} of Mukta bhasma as per OECD guideline falls under class four with no signs of acute toxicity with up to a maximum dose of 2000 mg/kg. No change in normal behavioral patterns or signs and symptoms of toxicity and mortality were observed up to this dose level.

Accelerated stability study was done as per the ICH guidelines for the formulation and it was observed after 21 days the appearance of tablet remained clear and no significant variation in pH was observed after subjecting the formulations to stability stress for 21 days at 40 °C and 75% relative humidity and there was no significant change in percentage Drug release that is 94.21% release after 21 days time period.

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