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FORMULATION, DEVELOPMENT AND STANDARDIZATION OF AN AYURVEDIC MUCO-ADHESIVE EXTENDED RELEASE VAGINAL TABLET

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ABSTRACT: The study aims to standardize a vaginal herbal formulation consisting of stem barks of *Ficus glomerata* Roxb. and *Symplocos racemosa* Roxb. Since they are used as Ayurvedic medicine and described in ancient text Charak Samhita as astringent, anti-inflammatory and treatment of vaginitis / leucorrhoea. This new herbal formulation is likely to exhibit significant antimicrobial action due to presence of phenolic and flavonoidic compounds. The extractive value was 1.64 and 1.70% w/w for aqueous and alcoholic extract. Total Phenol Content was 225.67 and 220.00 µg Gallic acid equivalent / mg for aqueous and alcoholic extract. Fifteen types of muco-adhesive tablets weighing 550, 700 or 900 mg each were prepared using combinations of research drug, Carbopol and Hydroxy-Propyl-Methyl Cellulose as polymers, talc as glidant, magnesium stearate as lubricant and Micro-Crystalline Cellulose and Lactose monohydrate as diluents. Similarly, five types of effervescent muco-adhesive tablets using sodium bicarbonate and citric acid in 3:1 ratio were prepared. Apart from weight, thickness, hardness and friability of each group, the surface pH, swelling index and muco-adhesive force were determined. The formulation F-XII provides best physical parameters of hardness (6.0 ± 2.53 kg/sq.cm), pH value (4.80 ± 0.04), swelling index (69.39 ± 0.44 % w/w) and muco-adhesive force (0.667 ± 0.02 Newton) which indicate its sustained slow releasing of anti-vaginitis drug delivery as an effective muco-adhesive vaginal tablet.

INTRODUCTION: Vaginitis is an inflammation of the vagina that can result in discharge, itching and pain.

The cause is usually a change in the normal balance of vaginal bacteria or an infection. Similarly, leucorrhoea refers to the medical condition where excessive abnormal thick and sticky white or yellowish discharge occurs from the vagina accompanied with inflammation and associated with symptoms like itching, burning sensation and pain followed by body ache and tiredness. The vagina is a fibro-vascular tube connecting the uterus to the outer surface of the body.

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The vaginal epithelium consists of a stratified squamous epithelium and lamina propia. In allopathic system of medicine, vaginal tablets have been prescribed for patients suffering from leucorrhoea indicated through symptoms of excessive white, sticky, foul-smelling vaginal discharge, known as Swetapradar in Ayurveda. Traditional commercial preparations, such as creams, foams, gels, suppositories, irrigations and tablets are known to reside in the vaginal cavity for a relatively short period of time owing to the self-cleaning action of the vaginal tract, and often require multiple daily doses to ensure the desired therapeutic effect. Therefore, the vaginal route appears to be highly appropriate for bio-adhesive drug delivery systems in order to retain drugs for treating largely local conditions¹. These drugs are transported across the vaginal membrane by the trans-cellular route, intra-cellular route or vesicular and receptor-mediated transport mechanisms. Bio-adhesives can control the rate of drug release and extend the residence time of vaginal formulations.

In this regard, mucosal drug delivery has received a great deal of attention over the past few decades. Further, the mechanism of extended drug release ensures that the active drug is released slowly over time from the tablet which has the advantage of taking medicine less often. Therefore, now-a-days muco-adhesive extended release vaginal tablets are very useful for treatment of Leucorrhoea where the tablets adhere on mucus membrane of inner vaginal wall and the active drug is released slowly within around 8 - 10 hours in vaginal fluid and inhibit the discharge by their antimicrobial activity²⁻⁴. This has the advantage that tablets need not be taken repeatedly or orally; they can be just inserted in the vagina at bed-time only.

Many herbal plants and their combinations in the nature of Ayurvedic drugs have been prescribed for oral administration and external application in the Ayurvedic text for the treatment of vaginitis or leucorrhoea. The aim of the present study was to standardize the new vaginal herbal formulation by mixing the equal parts of stem barks of *Ficus glomerata* Roxb. and *Symplocos racemosa* Roxb. because both these plants have been used since ancient times in the Ayurvedic system of medicine and elaborated in ancient texts such as Charak Samhita (Chikitsa Sthanam) as an astringent, anti-

inflammatory and haemostatic and useful for arresting excessive abnormal vaginal discharge⁵⁻⁷. This is a new herbal formulation which has not been evaluated till now although it is likely to exhibit sustained and significant antimicrobial action due to the synergetic effect of the phenolic and flavonoidic compounds present in this research drug and the pharmacological properties of its constituent herbs.

This research formulation contains the plant *Ficus glomerata* Roxb. or Cluster Fig which belongs to the Moraceae family. It is a moderate sized spreading lactiferous tree without much prominent aerial roots found throughout India whose fruits are eaten by villagers. Its leaves are dark green, ovate or elliptical while the fruits contain 2 - 5 cm diameter sub-globose and smooth receptacles. The fruits are orange and dull reddish when ripe and having a pleasant smell. The stem bark is 0.5 -1.8 cm. thick, grayish green in colour and having an uneven soft surface^{6,7}. On rubbing it, white papery flakes come out from the outer surface; the inner surface is light brown, fracture fibrous and mucilaginous taste.

The stem bark, fruits, leaves and latex of this plant have been used since ancient times as mentioned in the Ayurvedic text book for treatment of dysentery, diarrhoea, toothache, stomach-ache, vaginal disorders, menorrhagia, haemoptysis, diabetes, piles and glandular swelling, etc. The roots of the plant are used in dysentery, pectoral complications, and diabetes, and also applied in inflammatory glandular enlargement, mumps, and hydrophobia. The latex is externally applied on wounds to decrease inflammation, pain and edema and to promote healing. The Phytochemical compounds isolated from the stem bark are leucocyanidin-3-o-B-glucopyranoside, leucopelarogonidin 3-O-a-L-rhamnopyranoside, B-sitosterol, stigmasterol, tetracyclic triterpene- gluanol acetate and tiglic acid. The reported pharmacological properties of the different plant parts are hypoglycaemic, antiulcer, antioxidant, wound-healing, anti-inflammatory, anti-diarrhoeal, anti-bacterial, anti-fungal, antipyretic and anti-diuretic⁸.

Symplocos racemosa Roxb. known as Lodhra belonging to the Symplocaceae family is found distributed throughout North Eastern India up to

2,500 ft. elevation. It is a small evergreen tree with stem up to 6 m in height and 15 cm in diameter. Its stem bark is useful in bowel complaints such as diarrhea and dysentery, in dropsy, eye disease, liver complaints, wound healing, excessive vaginal discharge, menstrual problems, fevers, ulcers, scorpion-string, etc. The bark is often employed in the preparation of plasters and is reported to promote maturation or resolution of boils, stagnant tumors and other malignant growths. A decoction of the bark or wood is used as gargle for giving firmness to spongy and bleeding gums and relaxed uvula.

The phytochemical investigation of the n-butanol soluble fraction of the bark of stem of *Symplocos racemosa* Roxb. yielded two phenolic glycosides of salirepin series namely symplocuronic acid and symplocoside while salirepin has also been isolated from this plant⁹. The alcohol extract of stem bark indicated the presence of carbohydrates, glycosides, saponins, terpenoids and alkaloids while its ether extract indicated the presence of glycosides, phytosterol and steroids. The prominent pharmacological activities of its stem bark are antibacterial, anti-inflammatory, antiulcer, anti-tumor, antimicrobial and antioxidant¹⁰.

MATERIALS AND METHODS:

Plant Materials: The stem barks of *Symplocos racemosa* Roxb. and *Ficus glomerata* Roxb. were purchased from crude drug supplier of Katwa Chowrasta, Burdwan district for the preparation of herbal vaginal tablet and the plant samples were authenticated by the Research Officer, Botanical Survey of India, Howrah, India (Ref. No. BSI/CNH/SF/Tech./2016).

Chemicals used for Preparation of Tablets: Dicalcium phosphate, Gum acacia, Lactose monohydrate, Sodium carboxy-methyl-cellulose, Sodium starch glycolate, Starch (maize), Ferric Chloride (FeCl₃), Magnesium stearate (IP grade), Microcrystalline cellulose (IP grade), Talc (IP grade), Folin - Ciocalteu's reagent, Sodium carbonate and Sulphuric acid were obtained from M/s Merck Specialties Pvt. Ltd., Mumbai. Carbopol 934P and Hydroxy-propyl-methyl-cellulose K4M were purchased from reputed company M/s Hi Media Laboratories Pvt. Ltd., while Citric acid monohydrate was procured from

M/s B.D. Pharmaceutical works Pvt. Ltd., and Sodium bi-carbonate (IP grade) from M/s Indian Drug House.

Preparation of Extracts: The stem barks of *Symplocos racemosa* Roxb. and *Ficus glomerata* Roxb. were taken in equal quantity by weight, washed, sun dried and crushed to particle size of 40 mesh. This coarse powder was sequentially extracted with petroleum ether (60 °C - 80 °C), chloroform, acetone, ethanol and water using soxhlet apparatus. These extracts were filtered using a Buckner funnel and Whatman No. 1 filter paper at room temperature and concentrated at reduced temperature and pressure using rotary evaporator. All obtained extracts were stored in refrigerator below 10 °C for subsequent experiments. The aqueous extract of the research formulation was used in the study^{11, 12}.

Analysis of Phytochemical Constituents: The extract was standardized by using the standard methods for ascertaining the presence of different phyto-chemical constituents such as alkaloids, amino-acids, reducing sugars, tannins, saponins, anthroquinones, steroids, terpenoids, flavonoids and salicyclates.

Determination of Total Phenol Content: The total phenol content was determined using the Folin-Ciocalteu reagent. To 0.5 ml aliquot of dried aqueous extract, 2.5 ml of Folin- Ciocalteu's reagent (10%) and 2 ml of 7.5% sodium carbonate were added. The absorbance was read after 30 min incubation period at room temperature at 760 nm colorimetrically and calculation was done on the basis of standard calibration plot using known different concentrations of Gallic acid and Total phenolic content was expressed as mg Gallic Acid Equivalent (GAE)^{13, 14}.

Formulation of Drug-Free Tablets (i.e. Placebo): The drug-free (placebo) tablets were prepared using a mixture of polymers and microcrystalline cellulose with or without effervescent. Carbopol and Hydroxy-Propyl-Methyl Cellulose (HPMC) were used as the polymers. Tablets loaded with effervescent agent consisted of sodium bicarbonate and citric acid in 3:1 molecular ratio and produced gas bubbles in liquid media. All used chemicals were of analytical reagent grade.

The composition of the polymers and effervescent agents used in various placebo tablets is shown in **Table 1**. For the various drug-free formulations, the effect of effervescent agent on polymers' bio-adhesive characteristics was investigated. The performances of these bio-adhesive polymers were

evaluated, especially three main parameters pH value, swelling index and the bio-adhesive strength. On the basis of these data, suitable polymers were selected to prepare the bio-adhesive effervescent vaginal tablets of active research drug.

TABLE 1: COMPOSITIONS OF POLYMERS USED IN PLACEBO TABLETS

S. no.	Polymer used	Polymer weight (mg)	Effervescent Mixture (mg)
S1a	Carbopol 934P	150	0
S1b	Carbopol 934P	150	100
S2a	HPMC K4M	150	0
S2b	HPMC K4M	150	100
S3a	Sodium CMC	150	0
S3b	Sodium CMC	150	100
S4a	Carbopol + Sod. CMC	75+75	0
S4b	Carbopol + Sod. CMC	75+75	100
S5a	Sod.CMC + HPMC K4M	75+75	0
S5b	Sod.CMC + HPMC K4M	75+75	100

Preparation of Muco-adhesive Vaginal Tablets:

The various types of bio-adhesive vaginal herbal tablets were prepared using the dry compression technique of tablet preparation. During this study, 15 types of muco-adhesive herbal vaginal formulations and 5 types of muco-adhesive effervescent vaginal formulations were prepared for testing. All these formulations were prepared by mixing the same amount of the active research drug extract powder (500 mg) with different amounts of excipients, binders and developers. The polymers Carbopol and Hydroxy-Propyl-Methyl Cellulose were used as excipients, while talc and magnesium

stearate were added as glidant and lubricant respectively. Micro-Crystalline Cellulose and Lactose monohydrate were used as diluents¹⁵. The binder hydroxyl-propyl-methyl-cellulose was used to form sustained-release matrix with the polymer carbopol, which swells to form hydrogel-like matrices through which drug molecules could be released at a controlled rate¹⁶. Then all ingredients were passed through 44# mesh sieve and finally the mixture was compressed into tablet-form using single punch tablet compression machine. The ingredients in each type of muco-adhesive tablet are shown in **Table 2**.

TABLE 2: INGREDIENTS OF VARIOUS MUCO-ADHESIVE TABLETS

S. no.	Ingredients (mg)	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII	F-VIII	F-IX	F-X	F-XI	F-XII	F-XIII	F-XIV	F-XV
1	Active Research Drug (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
2	Carbopol 934P	25	12.5	10	-	-	-	-	25	20	35	35	15	45	25	15
3	Sodium Starch Glycolate	25	37.5	40	3	3	8	-	-	-	-	-	-	-	-	-
4	HPMC K4M	-	-	-	10	25	35	95	75	50	95	150	90	90	110	110
5	Starch (maize)	-	-	-	80	65	55	-	-	-	-	-	-	-	-	-
6	Gum Acacia	-	-	-	-	-	10	-	-	-	-	-	-	-	-	-
7	Lactose monohydrate	-	-	-	100	100	85	33	65	65	132	100	100	100	100	100
8	Di-Calcium Phosphate	-	-	-	-	-	-	65	28	58	128	-	-	-	-	-
9	Microcrystalline cellulose	-	-	-	-	-	-	-	-	-	-	95	175	145	145	155
10	Talc	-	-	-	7	7	7	7	7	7	10	10	10	10	10	10
11	Magnesium Stearate	-	-	-	-	-	-	-	-	-	-	10	10	10	10	10
	Total ingredients (mg)	550	550	550	700	700	700	700	700	700	900	900	900	900	900	900

Formulation of Effervescent Muco-adhesive Vaginal Tablets: The effervescent muco-adhesive vaginal tablets were also prepared by direct mixing of required quantity of 500 mg active research drug, effervescent (consisting of sodium bicarbonate and citric acid in the ratio of 3:1), polymers (*i.e.* carbopol, hydroxy-propyl-methyl cellulose and sodium carboxy-methyl cellulose), microcrystalline cellulose, magnesium stearate and

tal. Talc and magnesium stearate were added as glidant and lubricant respectively in the ratio of 2:1. Finally the mixture was compressed into tablets using single punch tablet compression machine. Each tablet of different effervescent formulation, *i.e.*, T-1 to T-5, contained 500 mg of active research drug and has an approximate weight of 900 mg as detailed in **Table 3**.

TABLE 3: COMPOSITION OF VARIOUS MUCO-ADHESIVE EFFERVESCENT VAGINAL TABLETS

S. no.	Ingredients	T-1	T-2	T-3	T-4	T-5
1	Active Research Drug	500	500	500	500	500
2	Carbopol 934P	75	–	75	60	–
3	HPMC K4 M	75	75	–	60	60
4	Sodium CMC	–	75	75	–	60
5	Sodium bi-carbonate	75	75	75	97.5	97.5
6	Citric acid	25	25	25	32.5	32.5
7	Microcrystalline cellulose	127.5	127.5	127.5	127.5	127.5
8	Talc	15	15	15	15	15
9	Magnesium Stearate	7.5	7.5	7.5	7.5	7.5
	Total (mg)	900	900	900	900	900

Evaluation of Muco-adhesive Vaginal Tablets:

All types of muco-adhesive vaginal tablets were tested and evaluated in respect of the following standard testing parameters:

Weight Variation: Ten tablets from each formulation were weighed using an electronic balance and the average weight was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in **Table 4** and none deviates by more than twice that percentage.

Thickness: The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper (Pico India). The average values were calculated.

Hardness of the Tablet: The tablet hardness, the force required to break a tablet in a diametric compression force, was estimated using a hardness tester (Pfizer type) to determine the need for pressure adjustments on the tablet machine. Hardness can affect the disintegration properties. So if the tablet is too hard, it may not disintegrate in the required period of time. The hardness of the tablets was determined using Monsanto hardness tester and expressed in kg/sq.cm. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability: Friability is a measure of the resistance of the tablets to abrasion. It is an important parameter which tests the breaking point and structural integrity of a tablet under conditions of storage, transportation and handling before usage. The breaking point of a tablet is primarily based on its shape. The friability of the tablets was measured using Friability Test Apparatus (Imcorp, India) by tumbling them in a rotating drum. After tumbling, the integrity of the tablets and the weight loss are evaluated. Ten tablets are weighed initially, rotated at 25 rpm for 4 min (total 100 rotations) and re-weighed after removal of fines. Friability below 1.0 % w/w was considered acceptable¹⁷.

$$\% \text{ Weight loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Determination of the Surface pH Value: Surface pH of the tablets was determined in order to investigate the possibility of any *in vivo* side effects. Since an alkaline pH may cause irritation to the vaginal mucosa, it was determined to keep the surface pH as close to the system pH (4.0 – 5.0) as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in

contact with the surface of the tablets and allowing it to equilibrate for 1 minute.

Swelling Study: The swelling behaviour of tablet can be described in terms of their water absorbing capacity with time. Tablets were initially weighed individually (W_0), placed separately in 2% agar gel plates and incubated at $(37 \pm 1)^\circ\text{C}$. At regular 0.5 hour time intervals until 4 hours, each tablet was removed from the Petri-dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (W_t) and the percentage of swelling were calculated using the following formula:

$$\% \text{ Swelling} = \{(W_t - W_0) / W_0\} \times 100$$

Where W_t is the weight of the tablet at time t and W_0 is the initial weight of the tablet. The swelling was calculated and plotted as a function of time. The slope of the linear plots was taken as the swelling rate¹⁸.

In-vitro Muco-adhesion Study: Several types of mucosa, including rat intestine, pig oral, bovine sublingual and goat vaginal mucosa have been used as model biological tissues for evaluation of bio-adhesion. A simple apparatus was devised to measure the minimum detachment force. In evaluation of adhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. In the present study, goat vaginal mucosa was used as a model mucosal surface for bio-adhesion testing. For this purpose, the mucosa was removed immediately after slaughter and kept in phosphate buffer.

At the time of testing, a section of mucosa was secured keeping the mucosal side out on the upper glass vial using rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1 cm. Then one vial with section of mucosa and another vial were fixed on height adjustable pan. To a lower vial, a tablet was placed with the help of bi-layered adhesive tape, adhesive side facing downward. The height of the lower vial was adjusted so that a tablet could adhere to mucosa on the upper vial. A constant force was applied on the upper vial for 2 min, after which it was removed and the upper vial was then connected to the balance. Then the weight on right side pan was slowly added in increments of 0.5 gm till the two

vials just separated from each other. The total weight required to detach the two vials was taken as a measure of the muco-adhesive strength^{19, 20}. From this muco-adhesive strength, the force of adhesion was calculated using the following formula:

$$\text{Force of adhesion (Newton)} = \text{Muco-adhesive Strength (gm)} \times 9.81/1000$$

RESULTS: Evaluation of the physical parameters of powder of the herbal vaginal formulation indicated that while the moisture content was 8.2% w/w, the total ash content was 12.30% w/w, the acid insoluble ash was 0.77% w/w and water soluble ash was 10.66% w/w. The extractive value of aqueous extract was 1.64% w/w and the extractive value of alcoholic extract was found to be 1.70% w/w. The phytochemical constituents like alkaloids, flavonoids, tannins and carbohydrates were found to be present in the aqueous and alcohol extracts of the Research Formulation.

The total phenol content (μg Gallic acid equivalent / mg of extract) was calculated from the absorbance calibration standard curve ($R^2 = 0.997$) generated with different concentrations of Gallic acid. The TPC was found to be 225.67 μg Gallic acid equivalent / mg of extract in the aqueous extract and 220.00 μg Gallic acid equivalent/mg of extract in alcoholic extract of the research formulation which could be directly responsible for its antimicrobial, anti-leucorrhoeal and astringent properties.

The present study examined the efficacy of various combinations of drug, excipients, polymers, *etc.* with the objective to develop a standardized vaginal tablet for curing bacterial, fungal and others vaginal infections and decreased the associated symptoms like excessive white discharge, itching, foul smell, *etc.* One critical parameter during these experiments was to maintain a pH of around 4.5 to 5.0 in the vaginal mucosa during prolonged periods of intervention by the bio-adhesive tablets to inhibit growth of pathologic organisms there.

The obtained results of the various parameters in respect of the 15 types of muco-adhesive and 5 types of effervescent muco-adhesive vaginal tablets have been presented in the **Tables 4 and 5** and **Fig. 1, 2, and 3**.

TABLE 4: PHYSICAL PARAMETERS OF MUCO-ADHESIVE VAGINAL TABLET FORMULATIONS

Formulation	Average Weight (mg)	Thickness (mm)	Hardness (kg/sq.cm)	Friability (% w/w)
F-I	562.1 ± 18.84	3.44 ± 0.02	2.0 ± 5.13	0.92
F-II	577.0 ± 10.39	3.60 ± 0.05	2.4 ± 11.34	0.90
F-III	563.2 ± 13.95	3.42 ± 0.02	1.8 ± 7.51	1.04
F-IV	756.1 ± 15.63	4.40 ± 0.03	2.2 ± 6.21	0.92
F-V	726.8 ± 22.27	4.06 ± 0.03	3.2 ± 4.46	0.85
F-VI	714.6 ± 19.36	4.22 ± 0.03	4.0 ± 8.74	0.87
F-VII	746.6 ± 26.39	4.38 ± 0.02	2.0 ± 7.28	0.97
F-VIII	735.8 ± 15.94	4.22 ± 0.01	3.4 ± 2.68	0.81
F-IX	706.0 ± 16.33	4.42 ± 0.02	3.8 ± 7.54	0.78
F-X	937.3 ± 18.95	6.00 ± 0.03	2.8 ± 11.31	0.89
F-XI	928.0 ± 42.20	5.82 ± 0.03	8.0 ± 4.52	0.42
F-XII	927.8 ± 25.30	5.80 ± 0.04	6.0 ± 2.53	0.66
F-XIII	932.2 ± 35.60	5.92 ± 0.05	5.6 ± 4.04	0.68
F-XIV	939.0 ± 28.21	5.66 ± 0.05	8.8 ± 6.69	0.38
F-XV	932.0 ± 25.82	5.78 ± 0.03	7.2 ± 8.14	0.35
ET-1	1000.0 ± 32.16	6.20 ± 0.03	6.4 ± 7.52	0.31
ET-2	1026.4 ± 36.15	6.40 ± 0.03	1.8 ± 5.39	1.08
ET-3	1005.7 ± 27.68	6.36 ± 0.06	3.0 ± 14.97	0.98
ET-4	983.3 ± 39.64	6.18 ± 0.04	6.2 ± 8.37	0.69
ET-5	979.6 ± 21.71	6.12 ± 0.04	2.6 ± 9.83	0.89

Number of tablets taken for each parameter (n = 10).

TABLE 5: OTHER PHYSICAL PARAMETERS OF MUCO-ADHESIVE VAGINAL TABLET FORMULATIONS

Formulation	Surface pH	Swelling Index at 24hour (%w/w)	Muco-adhesive force (Newton)
F-I	3.54 ± 0.11	23.92 ± 0.31	0.196 ± 0.04
F-II	3.50 ± 0.09	26.60 ± 1.95	0.118 ± 0.03
F-III	3.40 ± 0.11	131.00 ± 2.63	0.137 ± 0.03
F-IV	4.62 ± 0.04	62.01 ± 1.68	0.118 ± 0.03
F-V	4.78 ± 0.11	60.21 ± 2.84	0.177 ± 0.02
F-VI	4.56 ± 0.10	60.99 ± 5.37	0.177 ± 0.05
F-VII	4.70 ± 0.08	52.49 ± 0.99	0.235 ± 0.03
F-VIII	4.80 ± 0.09	78.00 ± 5.78	0.392 ± 0.03
F-IX	4.80 ± 0.06	61.03 ± 1.32	0.353 ± 0.05
F-X	4.72 ± 0.06	62.19 ± 2.24	0.589 ± 0.03
F-XI	4.68 ± 0.09	65.26 ± 0.62	0.706 ± 0.02
F-XII	4.80 ± 0.04	69.39 ± 0.44	0.667 ± 0.02
F-XIII	4.86 ± 0.05	67.89 ± 0.51	0.687 ± 0.03
F-XIV	4.88 ± 0.09	66.50 ± 1.69	0.647 ± 0.05
F-XV	4.79 ± 0.11	64.71 ± 2.14	0.647 ± 0.07
ET-1	4.50 ± 0.21	99.20 ± 5.16	0.216 ± 0.04
ET-2	4.42 ± 0.18	90.56 ± 1.82	0.177 ± 0.04
ET-3	4.48 ± 0.24	78.39 ± 3.61	0.255 ± 0.03
ET-4	4.38 ± 0.22	98.94 ± 3.24	0.255 ± 0.03
ET-5	4.40 ± 0.21	190.10 ± 7.81	0.157 ± 0.02

Number of tablets taken for each parameter (n = 3).

DISCUSSION: The vaginal micro-biota is dominated by Gram - positive Lactobacillus bacteria, which maintain the acidic pH in the vagina (pH 4.5) by converting glycogen from exfoliated epithelial cells into lactic acid and protect it from pathogen invasion by the production of organic acid, bacteriocins, and hydrogen peroxide. The ecology of the vagina is influenced by factors such as the glycogen content of epithelial cells, glucose, pH, hormonal levels, trauma during

sexual intercourse, birth-control method, age, antimicrobial treatment and delivery. The acidic environment of the vagina is a natural barrier to infection and irritation, since it represses the growth of bad bacteria which prefer a less acidic environment. Therefore, as long as the good bacteria count is high and the vaginal pH is acidic, bad bacteria have a very slim chance of overgrowing, making the chance of infection low. However, the pH changes with age, stages of

menstrual cycle, infections and sexual arousal while menstrual, cervical and uterine secretions and

semen act as alkalinizing agents and increase the pH²¹.

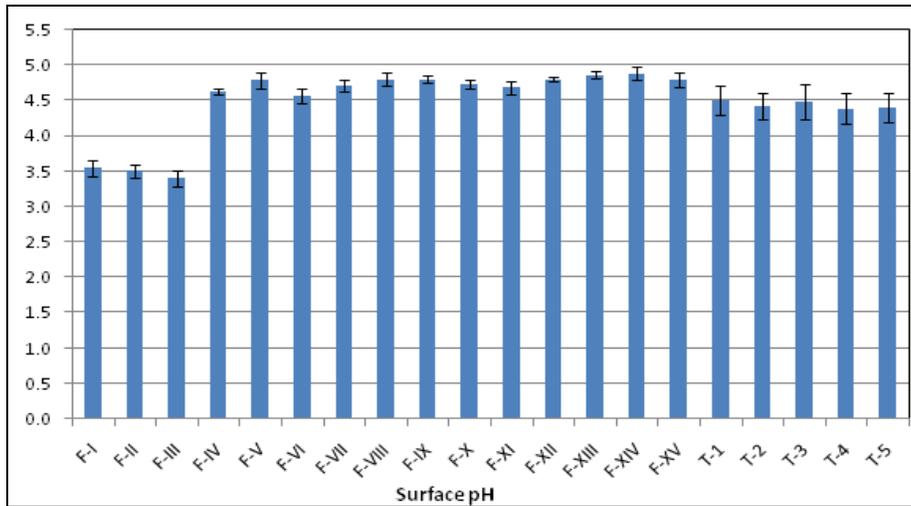


FIG. 1: SURFACE pH OF MUCO-ADHESIVE AND EFFERVESCENT VAGINAL TABLETS

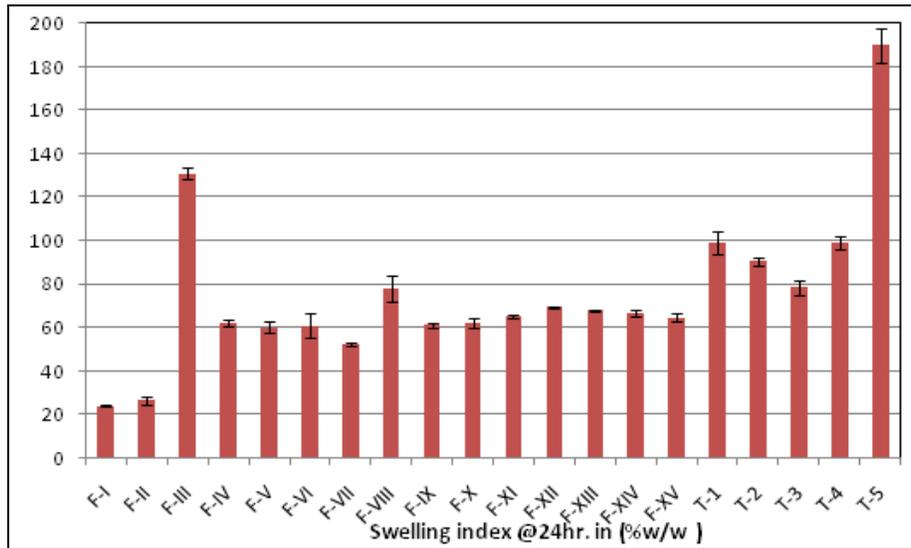


FIG. 2: SWELLING INDEX OF MUCO-ADHESIVE AND EFFERVESCENT VAGINAL TABLETS

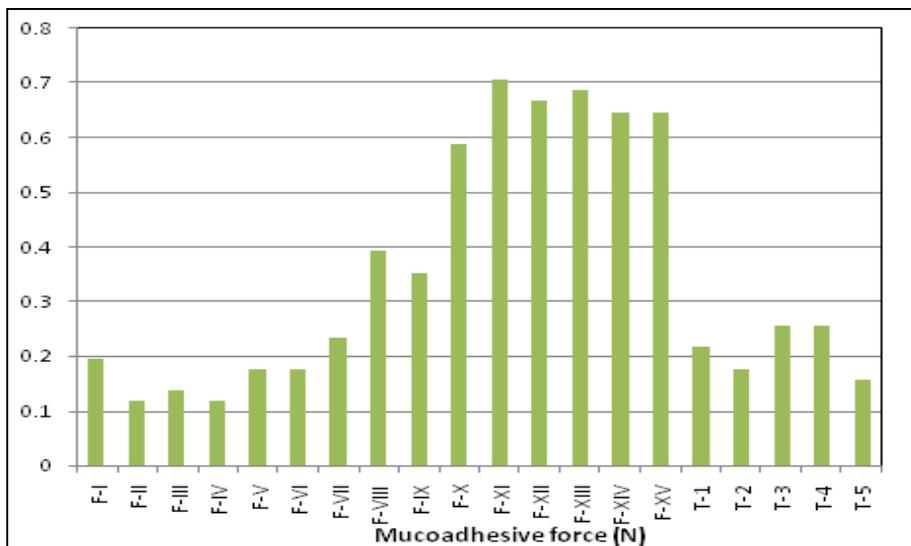


FIG. 3: BIOADHESIVE FORCE OF MUCO-ADHESIVE AND EFFERVESCENT VAGINAL TABLETS

The drug-free tablets were prepared using the mixture of polymer and microcrystalline cellulose (MCC) with or without effervescent. Carbopol 934P (CP) is a muco-adhesive polymer which has been investigated as a useful adjuvant for bio-adhesive drug delivery system. However, the drug release rate from the solid formulation of CP is slow. At the same time, swelling is also important for the assessment of adhesion. Shortly after swelling, adhesion does occur, but with a weak bond formed. To develop maximum adhesion strength, an optimum water concentration was needed for polymer particles. The porous channels increased the area of contacting between polymer particles and water so that the polymers could be hydrated more easily.

It has been observed that the first three muco-adhesive vaginal formulations, *i.e.*, F-I, F-II and F-III, were prepared by mixing of a single polymer (Carbopol) in various ratios as a disintegrating agent, and Sodium Starch Glycolate for developing muco-adhesive action with the active drug ingredient. The best outcomes were observed in case of F-III having average weight 563.2 ± 13.95 mg, thickness 3.42 ± 0.02 mm, hardness 1.8 ± 7.51 kg/sq.cm, friability 1.04% w/w, surface pH 3.40 ± 0.11 , swelling Index at 24 hour $131.00 \pm 2.63\%$ w/w and muco-adhesive force of 0.137 ± 0.03 Newton. After three trials of each of these 3 formulations, they were not considered feasible due to quick disintegration, less pH value, more swelling index and less muco-adhesive tension.

The next set of formulations, F-IV to F-VI, were prepared as standard muco-adhesive sustained release herbal vaginal drug delivery system in the form of tablets by mixing of the same concentration of active ingredient of research drug (500 mg) with various ratios of the polymers such as Hydroxy-Propyl-Methyl Cellulose (HPMC K4 M) to get sustained release property along with a binder (maize starch), sodium starch Glycolate (SSG), diluent (Lactose monohydrate) and glident (Talc) to increase total weight of tablets up to 700 mg. Only in case of F-VI, *Gum acacia* was added to increase its binding properties.

In this group of formulations, the best parameters were exhibited by formulation F-VI having 714.6 ± 19.36 mg average weight, 4.22 ± 0.03 mm

thickness, 4.0 ± 8.74 kg/sq.cm hardness, 0.87% w/w friability, 4.56 ± 0.10 surface pH, $60.99 \pm 5.37\%$ w/w swelling Index at 24 hour and 0.177 ± 0.05 Newton muco-adhesive force. However, the formulation F-VI has not been considered as feasible due to its low hardness and muco-adhesive tension.

Another set of formulations, F-VII, F-VIII and F-IX, were developed by adding various concentrations of the polymers specially Carbopol 934P, Hydroxy-Propyl-Methyl Cellulose (HPMC K4 M), diluent Di-Calcium Phosphate (DCP), Lactose monohydrate and talc to the research drug. The best physical parameters in this set were obtained in case of formulation F-IX having average wt 706.0 ± 16.33 mg, thickness 4.42 ± 0.02 mm, hardness 3.8 ± 7.54 kg/sq.cm, friability 0.78% w/w, surface pH 4.80 ± 0.06 , swelling index at 24 hour $61.03 \pm 1.32\%$ w/w and muco-adhesive force 0.353 ± 0.05 Newton. However, the formulation F-IX was not found very feasible due to high friability and low muco-adhesive strength.

The other set of drug formulations, F-X to F-XV were developed keeping the weight of the vaginal tablets around 900 mg by mixing 500 mg of the active ingredient drug with different proportions of polymers like Carbopol 934P, HPMC K4M, Di-Calcium Phosphate, Lactose monohydrate, talc, magnesium stearate, *etc.* After many trials and assessments, the best physical parameters are obtained in case of formulation F-XII which exhibits average weight 927.8 ± 25.30 mg, thickness 5.80 ± 0.04 mm, hardness 6.0 ± 2.53 kg/sq.cm, friability 0.66 %w/w, surface pH 4.80 ± 0.04 , swelling index at 24 hour $69.39 \pm 0.44\%$ w/w and muco-adhesive force of 0.667 ± 0.02 Newton.

The effervescent muco-adhesive vaginal tablets, ET-I to ET-V, were prepared by adding specific effervescent polymers like sodium bicarbonate and citric acid, along with Talc and magnesium stearate with the active research drug. The swelling rate was noticed to be increasing with increasing amount of effervescent being applied to the formulation, however, the hardness and muco-adhesive tension were found to have decreased. The phenomenon of increasing swelling could be explained by the good disintegration effect of effervescent, which made tablets increase in

volume and weight and led to construction of porous channels on the surface and inside of tablets²². The porous channels increased the area of contact between the polymer particles and water so that the polymers could be hydrated more easily. Among effervescent muco-adhesive vaginal tablets, the best results were noticed in ET-V formulation, which are average wt 979.6 ± 21.71 mg, thickness 6.12 ± 0.04 mm, hardness 2.6 ± 9.83 kg/sq.cm, friability 0.89% w/w, surface pH 4.40 ± 0.21 , swelling index at 24 hour $190.10 \pm 7.81\%$ w/w and muco-adhesive force 0.157 ± 0.02 Newton.

In order to achieve the desirable therapeutic effect, a good vaginal delivery system for curing vaginitis needs to reside at the site of infection for a prolonged period. Hence there is need to develop an effective drug delivery system that should prolong the contact of drug with vaginal mucosal surface. Thus vaginal tablets appear to be useful dosage forms as they are easy to apply, portable and provide effective local absorption. During this study, the formulation F-XII provides the best physical parameters such as hardness, pH value, swelling index and bio-adhesive tension which are essential for maintaining the vaginal flora. The results indicate that this formulation F-XII will provide sustained slow releasing of anti-vaginitis and anti-leucorrhoeal drug delivery system in the form of an effective muco-adhesive vaginal tablet.

CONCLUSION: The study suggests that the various relevant physical parameters of a vaginal herbal formulation which directly impact its efficacy and therapeutic action in respect of vaginitis can be suitably controlled and modified by varying the composition of its constituents such as active drugs, polymers, muco-adhesive agents, diluents, glidants, etc. The herbal formulation comprising of the aqueous extract of stem barks of *Symplocos racemosa* Roxb. and *Ficus glomerata* Roxb. exhibits the best therapeutic efficacy in the form of non-effervescent muco-adhesive tablet F – XII as indicated by its hardness, friability, pH, swelling index and muco-adhesive force.

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CONFLICT OF INTEREST: Nil

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