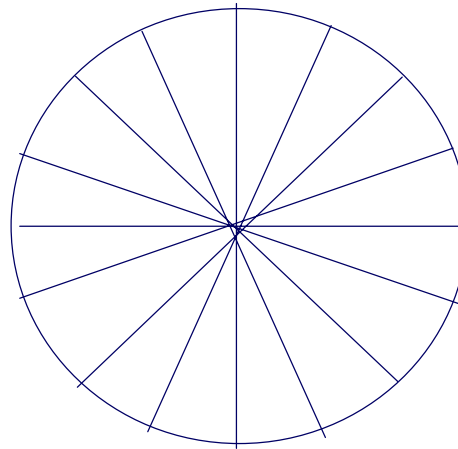


SURVEY OF MARKETED VAGINAL FORMULATIONS IN INDIA



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NIPER



- ❖ **National Institute of Pharmaceutical Education and Research**
- ❖ First national level institute in the field of pharmaceutical sciences in India, declared as an **institute of national importance** through an act of parliament
- ❖ The institute is an **autonomous body**
- ❖ Conceived to be the centre of excellence in pharmaceutical education and research
- ❖ **Projects ongoing with various international (WHO, CONRAD) and national (DST, DBT, ICMR, MHFW, CSIR) agencies and pharmaceutical industry**

VAGINA – ROUTE OF DRUG DELIVERY

- **Local and systemic delivery, uterine targeting of drugs**
- Growing interest in vaginal microbicide formulations
- **Vaginal dosage forms (VDFs): Tablets, capsules, gels, creams, films, tampons, suppositories, sponges, rings, foams**
- Acceptability of VDFs vary in different regions (cultural, climatic and socio-economical conditions)
- **Critical considerations during formulation development: selection of an appropriate dosage form and desired characteristics**
- Consumer preference studies in various countries (Brazil, Zimbabwe, Thailand, Cote d' Ivoire, USA)
- **No consumer preference study in India: practical difficulties in collecting information**

OBJECTIVES

- ❑ **Survey of marketed vaginal preparations available in India**
- ❑ **Evaluation of physico-chemical properties of selected formulations**

FIRST PHASE - SURVEY

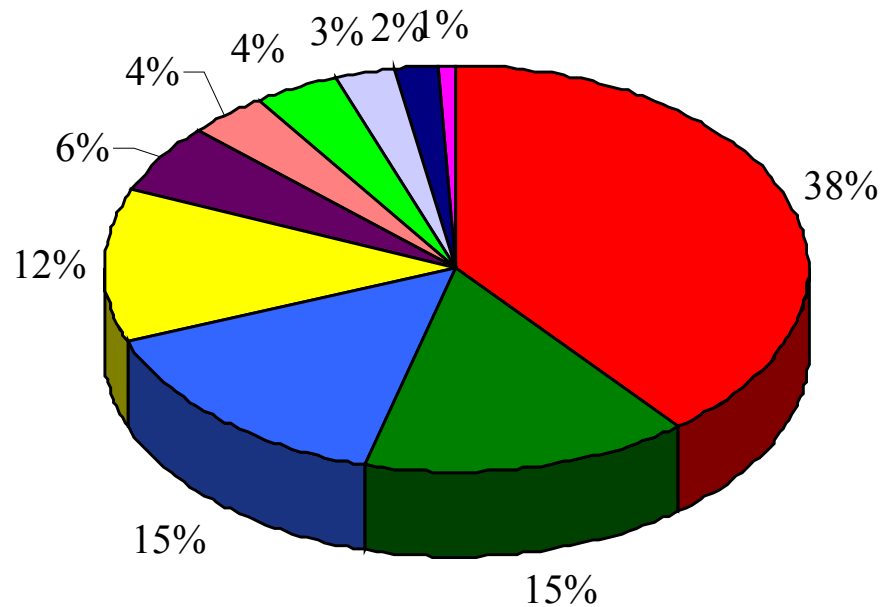
Collection of information about marketed vaginal preparations

- ✓ **Handbooks for pharmacists and physicians**
 - Current index of medical specialties (CIMS)
 - Monthly index of medical specialties (MIMS)
 - Indian Drug Review (IDR)
 - Drug Today
 - Indian Pharmaceutical Guide (IPG)
 - Information leaflets and labels of products.
 - Pharmacies/Chemist shops
- ✓ **The information collected includes brand name, active ingredients and their strength, type of dosage form, dosage schedule, indication, packing, and price**

VAGINAL FORMULATIONS IN INDIAN MARKET

TOTAL PREPARATIONS - 108

ALLOPATHIC - 105; HERBALS - 3



■ Tablets

■ Solutions

■ Soft gelatin capsules

■ Suppositories

■ Creams

■ Ointments

■ Pessaries

■ Gels

■ Ovules

■ Douches

APPLICATORS

✓ Prefilled applicators

- Lactal gel (lactic acid and glycogen in a gel base)
- Ortho applicator (a semisolid formulation of Clotrimazole)
- Cerviprime (sterile formulation of Dinoprostone gel)
- Vagifem® (tablets containing 17 β -Oestriol)

✓ Several products contain disposable or reusable applicators in secondary packing

ACTIVE INGREDIENTS

- ❖ **Anti-fungal agents** - Clotrimazole, Econazole, Miconazole, Metronidazole, Tinidazole, and Ketoconazole
- ❖ **Antibiotics** - Chloramphenicol, Neomycin, Hamycin, Natamycin, Nystatin, Tetracycline, Amphotericin-B, Sulphacetamide, Sulphadimidine, Sulphadiazine, Sulphathiazole, and Sulphabenzamide
- ❖ **Other anti-infective agents** - Povidone-iodine, Benzylamine, Ciclopirox olamine, and Chloroquinaldol
- ❖ **Estrogens and progesterones** – 17- β -Oestriol, Dienoestrol, Progesterone, and Dinoprostone
- ❖ **Contraceptives** – Nonoxynol-9
- ❖ **Lactic acid and Lactobacillus spores**
- ❖ **Plant extracts**

INDICATIONS

❑ Infections

Specific and non-specific vaginal infections (due to bacteria, fungi, and protozoa), cervical and vulval infections, prevention of recurrent infection of vagina and lower urinary tract

❑ Hormonal disorders

Endometriosis, leucorrhoea, postmenopausal vaginitis, cervical priming, induction and augmentation of labor, supplementation of luteal phase in case of sterility due to luteal deficiency, treatment of threatened abortions, dyspareunia after menopause and vaginal surgery, puerperal depression and to help pregnancy

❑ Dryness, discomfort and itching

❑ Contraception

❑ Lubrication

DOSAGE REGIMEN

- ❖ **Anti-infective products: once or twice daily for 1 to 14 days (usually once a day for 3-7 days)**
- ❖ **Some products: endo-cervical portion of genital tract**

COST

- ❖ **Average cost of a complete therapy – approx INR 60 (equivalent to 1.20 US\$)**
- ❖ **Anti-infective agents are comparatively less expensive than hormonal products (containing estrogens, progesterone, and synthetic analogues)**

SECOND PHASE - EVALUATION

Selected marketed products

Brand Name	Manufacturer or Marketer	Composition	Strength (mg)	Indication	Dosage regimen
CANDID V6	Glenmark Pharmaceuticals Ltd.	Clotrimazole	100	Candidiasis, vulvitis, mycosis, postmenopausal vaginitis	100 mg pessary for 6 nights
CLOMAX V7	Bombay Tablets Mfg Co.	Clotrimazole	100	Same as above	Same as above
CANESTEN 6	Bayer (India) Ltd. Health	Clotrimazole	100	Same as above	Same as above
GYNOSTATUM	Croslands Research Labs Ltd.	Clotrimazole	100	Same as above	1 pessary for 6 nights
INFA V	Lark Labs (India) Ltd.	Clotrimazole, Metronidazole, Lactobacillus sporogenes	100 + 500 + 150 million spores	Vaginitis (mixed, trichomonal, candidal and bacterial)	1 tablet daily for 8 consecutive days
CANDIZOLE T	Foreva (Unichem Labs Ltd.)	Tinidazole, Miconazole, Neomycin	500 200 20	Vaginitis, cervicitis	1 tablet preferably at bed time for 8 consecutive days
BETADINE Vaginal	Win Medicare Ltd.	Povidone iodine	200	Candidiasis, non specific vaginitis	1 pessary both in the morning and at night upto 14 days

VAGINAL TABLETS – PHYSICAL PROPERTIES

Product	Color	Shape	Weight* (gm)	Size, lxb (cm ²)	pH	
					Water	SVF _M
Candid V6	Off white	Caplet	1.019 ± 0.01	2.0 × 1.0	4.78	4.84
Clomax V7	Off white	Caplet	1.031 ± 0.05	2.0 × 1.0	4.81	4.29
Gynostatum	Off white	Caplet	1.212 ± 0.01	2.0 × 1.0	3.55	3.93
Canesten 6	Off white	Caplet	1.678 ± 0.02	2.5 × 1.0	4.91	4.96
Infa V	Off white	Caplet	1.110 ± 0.13	2.0 × 1.0	3.61	3.93
Candizole T	Off white	Almond	1.286 ± 0.03	2.1 × 1.3	4.71	4.19
Betadine	Brown	Almond	1.289 ± 0.02	2.1 × 1.3	3.60	3.35

* Mean of n = 3 ± Standard deviation

- **Size** - Vernier Calipers (Mituyoto, Japan)
- **Shape and color** - Visual observation
- **Weight** – Weighing balance (Mettler Toledo PR 2003 Delta range, d-0.001g)



VAGINAL TABLETS – PHYSICAL PROPERTIES

Product	Hardness* (kP)		Disintegration time* (Seconds)	
	Longitudinal axis	Radial axis	Water	SVF _M
Candid V6	11.6 ± 1.73	49.6 ± 0.1	120.8 ± 26.9	249.2 ± 69.4
Clomax V7	12.9 ± 1.76	44.57 ± 8.8	47.0 ± 10.9	214.7 ± 30.0
Gynostatum	9.77 ± 1.27	32.87 ± 1.1	71.7 ± 6.1	191.7 ± 8.0
Canesten 6	12.8 ± 1.74	49.7 ± 0.0	161.6 ± 59.8	425.7 ± 73.4
Infa V	24.6 ± 3.72	49.7 ± 0.05	105.0 ± 20.6	253.7 ± 9.3
Candizole T	6.07 ± 1.90	3.97 ± 0.5	52.2 ± 8.1	216.5 ± 22.9
Betadine	16.4 ± 2.25	13.8 ± 1.6	1249 ± 43.7	1605.8 ± 141.9

* Mean of n = 3 ± Standard deviation

- **Hardness** - Erweka Hardness Tester TH20, Hardness measured along both longitudinal and radial axes
- **Disintegration Test** - In 10 ml of water and SVF at 37°C

VAGINAL TABLETS – PHYSICAL PROPERTIES

Product	Viscosity (cPs)		Osmotic pressure* (mmol/kg)	Insoluble content# (%w/w)
	Water	SVF _M		
Candid V6	2.66	3.92	262 ± 12.12	51.9 ± 0.10
Clomax V7	2.60	3.53	88 ± 9.17	74.13 ± 5.56
Gynostatum	2.59	3.64	226 ± 9.64	52.63 ± 1.83
Canesten 6	3.10	3.99	516.3 ± 11.2	36.87 ± 1.75
Infa V	2.33	3.53	157 ± 6.0	69.10 ± 2.29
Candizole T	2.38	3.51	181.3 ± 3.5	66.3 ± 1.35
Betadine	2.56	3.38	152.3 ± 15.5	17.63 ± 1.81

* Mean of n = 3 ± Standard deviation

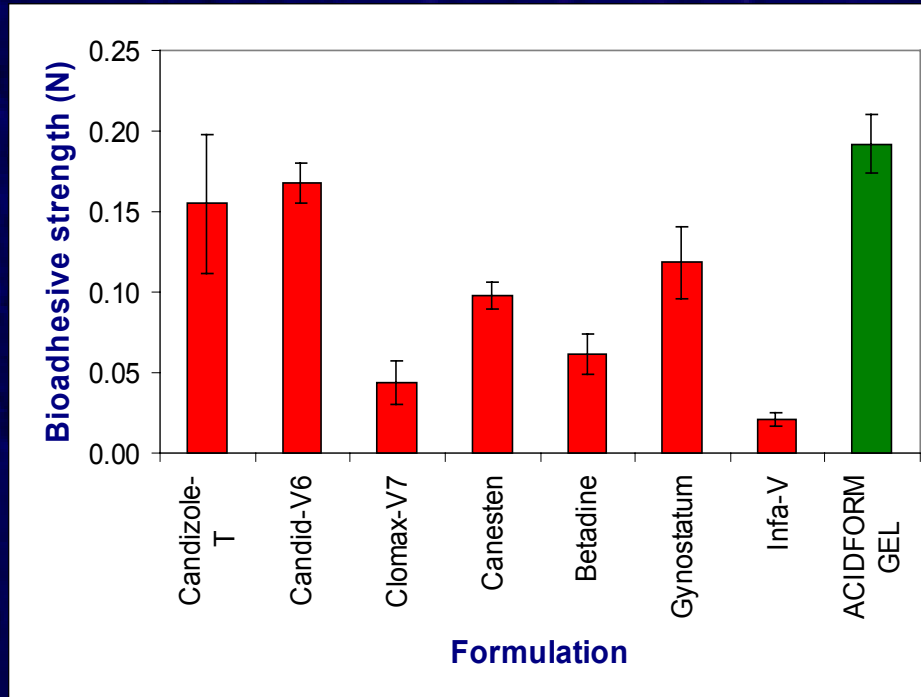
- Viscosity - Brookfield RVDV III+ Programmable Rheometer with coaxial cylinders (spindle – ULA 40Y), 1 tablet dispersed in 10 ml of fluid (water and SVF_M), spindle rotated at 250 rpm for 1 minute, at 37°C
- Osmotic Pressure - Vapor Pressure Osmometer 5520, Wescor, 1 tablet dispersed in 10 ml of water, filtered through Whatman No. 1 filter, 10 µl sample, calibration with OPTI-MOLE™ 290 mmol/kg osmolality standard
- Insoluble Content – 1 tablet dispersed in 10 ml of water, filtered through Whatman No. 1 filter, filter cake dried at 50°C for 4 hours and weighed

$$\% \text{ insoluble content} = (\text{Residue weight/Weight of 1 tablet}) \times 100$$

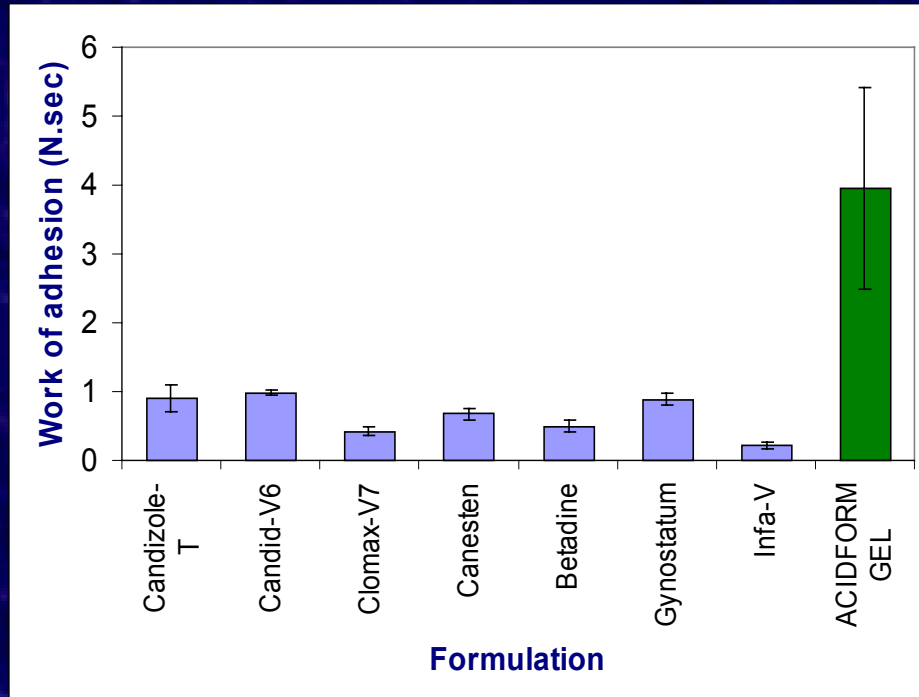


BIOADHESION OF VAGINAL TABLETS

Bioadhesive strength



Work of adhesion



Principle

Force required to break the adhesive bond between model membrane and the formulation - bioadhesive strength

Model membranes

Sheep vaginal mucosa

Texture analyzer

Modified probes for membranes in horizontal direction

CONCLUSIONS

- ❖ **Tablets are the most common and widely used VDFs in India**
- ❖ Formulations are available in various colors, sizes and possess wide range of physico-chemical parameters
- ❖ **Selected tablets possess poor bioadhesive properties, emphasizing the need of bioadhesive vaginal formulations**
- ❖ Novel vaginal formulations with optimized physico-chemical characteristics need to be developed
- ❖ **Help formulation scientists to determine desired characteristics of vaginal formulations targeted for Indian population and other tropical countries**

ACKNOWLEDGEMENTS

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- ❑ **Global Microbicides Project (GMP), CONRAD, USA - for bioadhesion studies**



INDIAN CENTER FOR TOPICAL MICROBICIDES

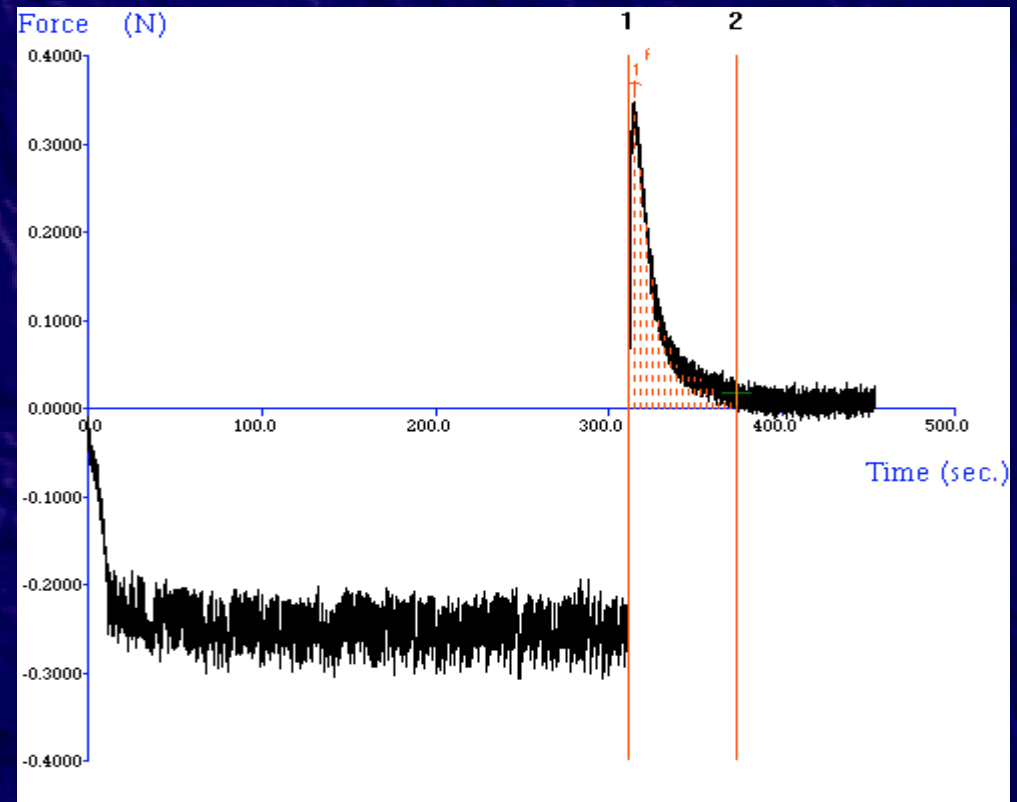
Thank You



BIOADHESION MEASUREMENT (Texture Analyzer)

Test parameters

- ✓ Pre-test speed – 0.3 mm/sec
- ✓ Test speed – 0.1 mm/sec
- ✓ Post-test speed – 0.1 mm/sec
- ✓ Force – 0.25 N
- ✓ Contact time – 5 minutes
- ✓ Load cell – 5 kg



Representative graph

MODIFIED SIMULATED VAGINAL FLUID

Ingredients	Amount per Liter
NaCl	3.51 gm
KOH	1.4 gm
Ca(OH) ₂	0.222 gm
Bovine serum albumin	0.018 gm
Lactic acid	2.0 gm
Acetic acid	1.0 gm
Glycerol	0.16 gm
Urea	0.4 gm
Glucose	5.0 gm
Mucin (type III, partially purified from porcine stomach)	15.0 gm
DM water	to 1000 ml
1N HCl	to adjust pH 4.2