# EFFECT OF DIFFERENT BIOADHESIVE POLYMERS ON PERFORMANCE CHARACTERISTICS OF VAGINAL TABLETS

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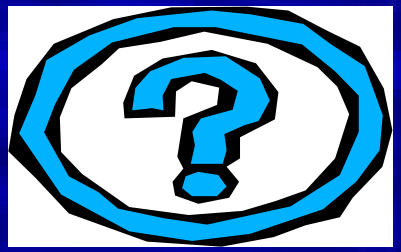
# Tablets as Vaginal Dosage Form

- Tablets comprise of 34% of all the marketed vaginal dosage forms in India*
- Convenient to user
- Non-sticky and easy to administer
- Stable in extremes of temperature and humidity (India, a Zone IV country, as per ICH guidelines)
- Socially, culturally, and economically acceptable

* As on January 2002

# Why Fast Disintegrating, Bioadhesive Tablets?



☹ **Limitations of conventional tablets**

- Longer disintegration time, thus delayed therapeutic effect
- Lack of bioadhesion, retention, and optimum spreading
- Need for frequent administration due to poor retention of the dosage form

☺ Novel fast disintegrating, bioadhesive tablets disperse rapidly in the vaginal cavity, form a smooth dispersion and coat cervico-vaginal surface efficiently

# Bioadhesive Polymers*

| Polymer | Route of administration |
|---|---|
| Carbopol 934P | Buccal, nasal, gastrointestinal, vaginal (Replens) |
| Polycarbophil AA1 Noveon | Nasal, buccal, ophthalmic vaginal (Rejoice, Replens) |
| Xanthan gum, Xantural | Buccal, nasal, gastrointestinal vaginal (LASRS) |
| Hydroxypropyl cellulose, Klucel | Buccal, nasal, ophthalmic vaginal |

**Vermani K, Garg S, and Zaneveld LJD Assemblies for *in vitro* measurement of bioadhesive strength and retention characteristics in simulated vaginal environment, *Drug Dev. Ind. Pharm*., in press**

- Bioadhesion, retention, and rheology are direct functions of polymers used in the formulation
- Dispersion time and pH can be modulated using specialty excipients
- Bioadhesive polymers known in literature may not yield similar results at all mucosal sites

# Work Plan

Preparation of tablets

Dry Granulation

Hardness, friability, dimensions, weight, and disintegration

Physical evaluation

Performance evaluation

Rheology, pH, bioadhesion, and osmolality of dispersions

# Tablet Manufacturing

- Selection of technique - **Dry Granulation**
- Polymers (5% w/w)
  - Carbopol 934P (CP)
  - Polycarbophil AA1 (Noveon, PC)
  - Hydroxypropyl methylcellulose, (Methocel K4M, HPMC)
  - Xanthan gum (Xantural, XG)
  - Sodium carboxymethylcellulose (Reliance Cellulose, SCMC)
  - Hydroxypropyl cellulose (Klucel, HPC)
- Methodology
  - Polymers + other excipients

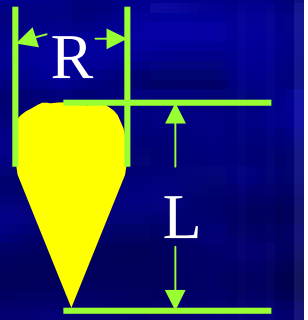
# Weight of Tablets

Indian Pharmacopoeia 1996 method used to determine weight variation

| Polymer / Test | CP | PC | HPMC | XG | SCMC | HPC |
|---|---|---|---|---|---|---|
| Weight (gm) Mean ± SD | 1.206 ± 0.027 | 1.224 ± 0.903 | 1.221 ± 0.021 | 1.203 ± 0.017 | 1.219 ± 0.027 | 1.169 ± 0.025 |

All tablets were found to have weights in the acceptable range

# Hardness and Friability




- Hardness of tablets was measured along both the radial and longitudinal axis (kP)
- Friability as specified in BP 2000

| Polymer / Tests | CP | PC | HPMC | XG | SCMC | HPC |
|---|---|---|---|---|---|---|
| Hardness (L) | 7.267 | 11.62 | 10.67 | 11.17 | 7.167 | 9.1 |
| Hardness (R) | 7.967 | 9.9 | 8.9 | 9.73 | 7.833 | 8.167 |
| Friability % (Limit) | 0.684 (<1%) | 0.341 (<1%) | 0.580 (<1%) | 0.640 (<1%) | 1.157 (<1%) | 0.844 (<1%) |

# Disintegration Test (DT) and pH Measurement

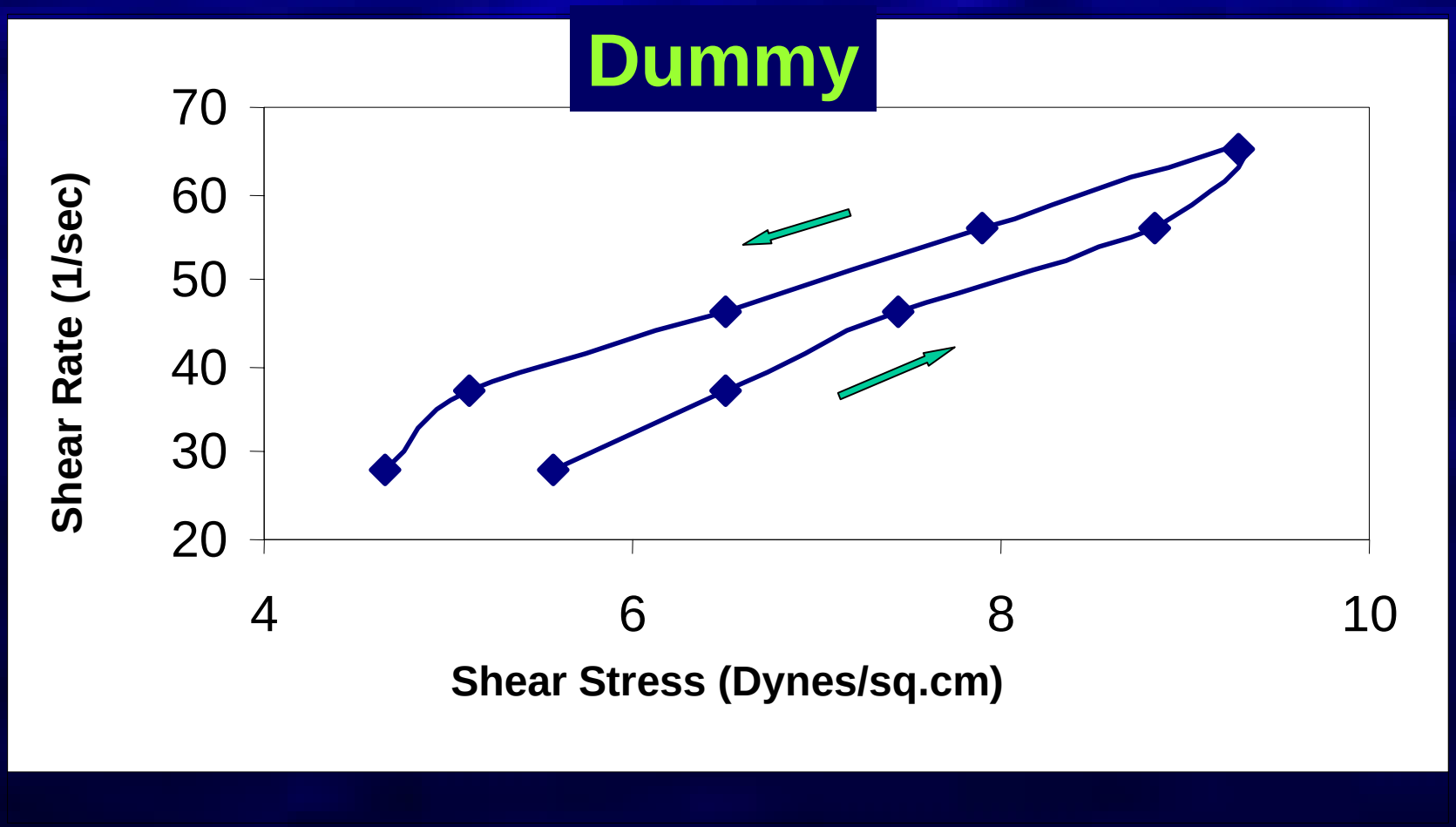
Tablet was placed in water (10 ml) and stirred at 300 rpm at 37ºC. Time taken for the tablet to disintegrate completely was recorded.

The pH of dispersions prepared in $SVF_M$ and water was also measured.

| Polymer / Tests | CP | PC | HPMC | XG | SCMC | HPC |
|---|---|---|---|---|---|---|
| DT | 12 Hr | 3.3 Hr | 60 sec | 24 Hr | 0.5 Hr | 28 sec |
| pH (Water) | 4.47 | 4.5 | 6.05 | 6.4 | 6.45 | 6.11 |
| pH ($SVF_M$) | 4.08 | 4.08 | 4.81 | 4.5 | 4.87 | 5.1 |

CP and PC yielded acidic dispersions

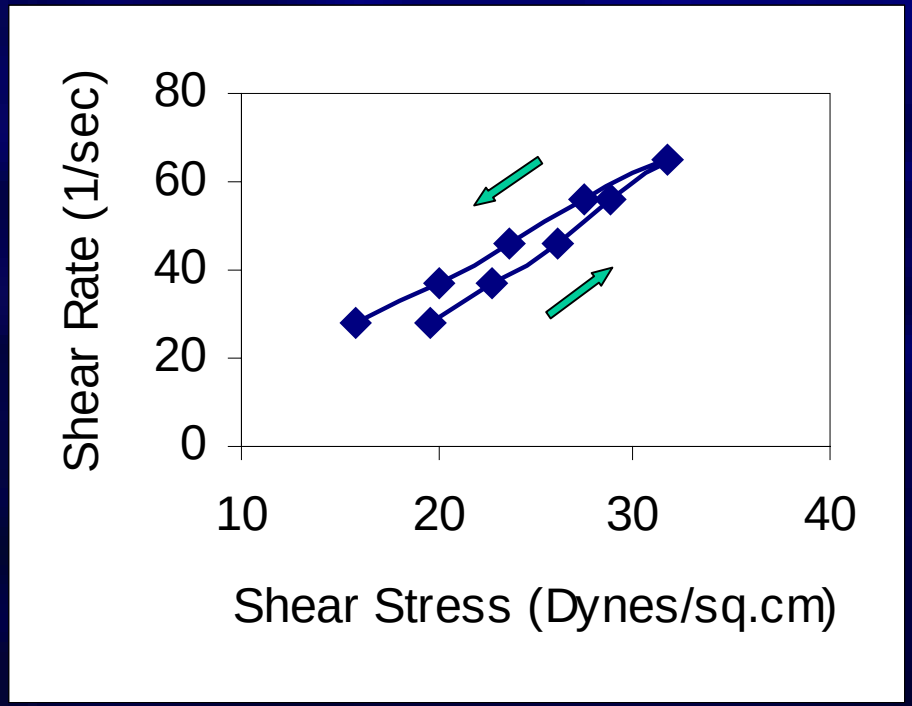
# Rheology of Tablet Dispersions



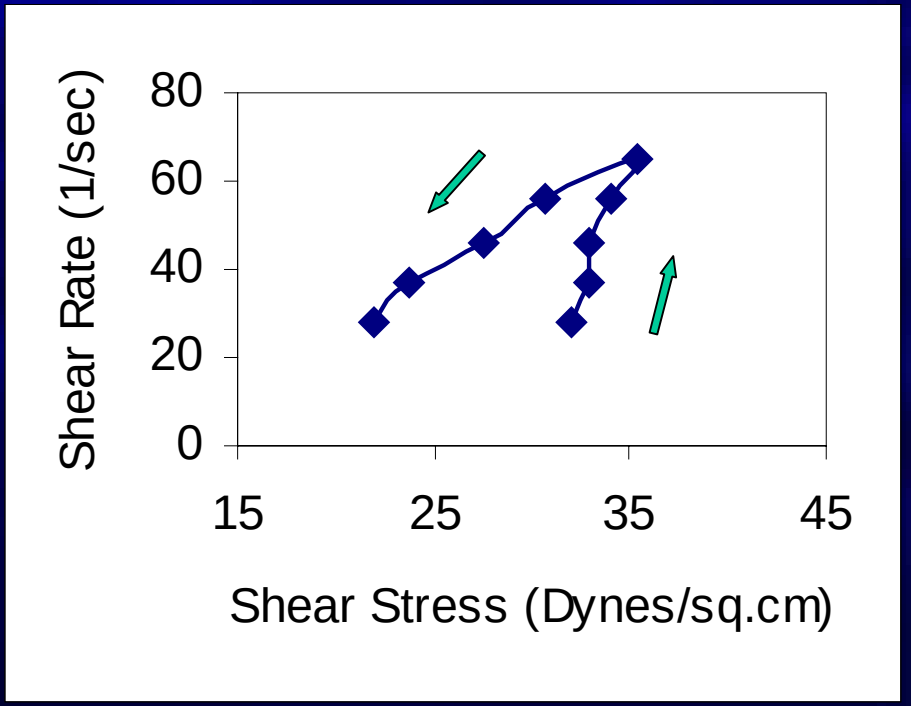

Pseudoplastic, thixotropic behaviour

# Rheology of Tablet Dispersions

**SCMC**



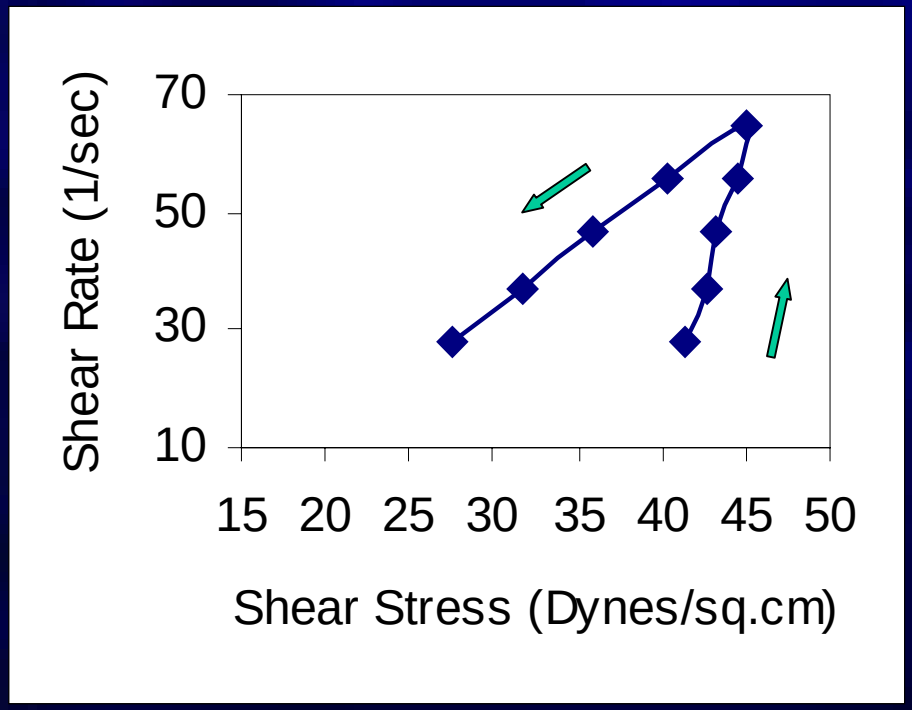

**PC**



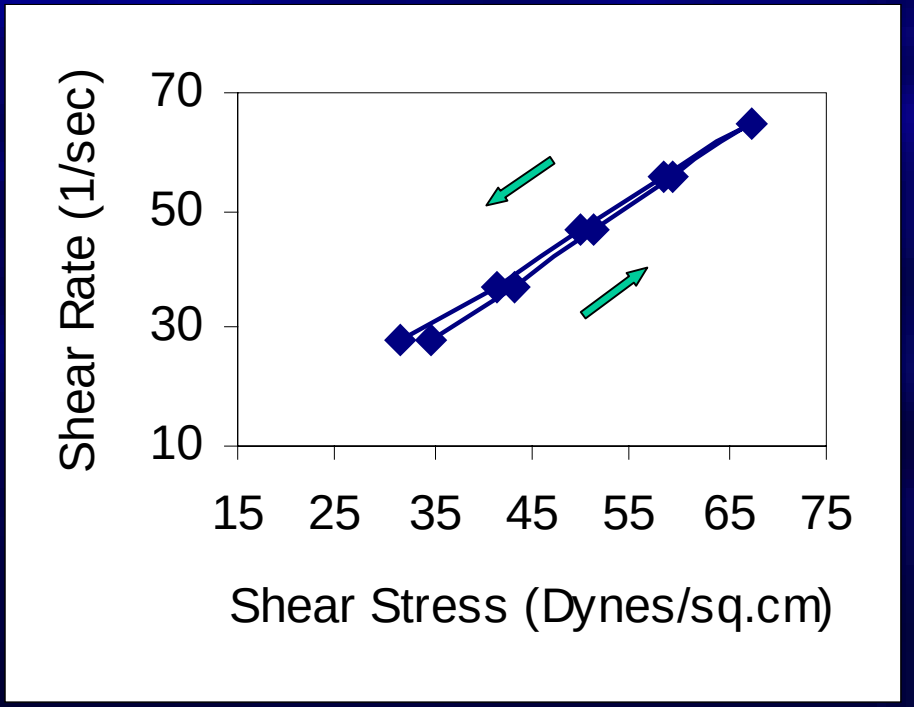

SCMC = Pseudoplastic, thixotropic behaviour
PC = Pseudoplastic, thixotropic, loss of internal structure

# Rheology of Tablet Dispersions

## CP



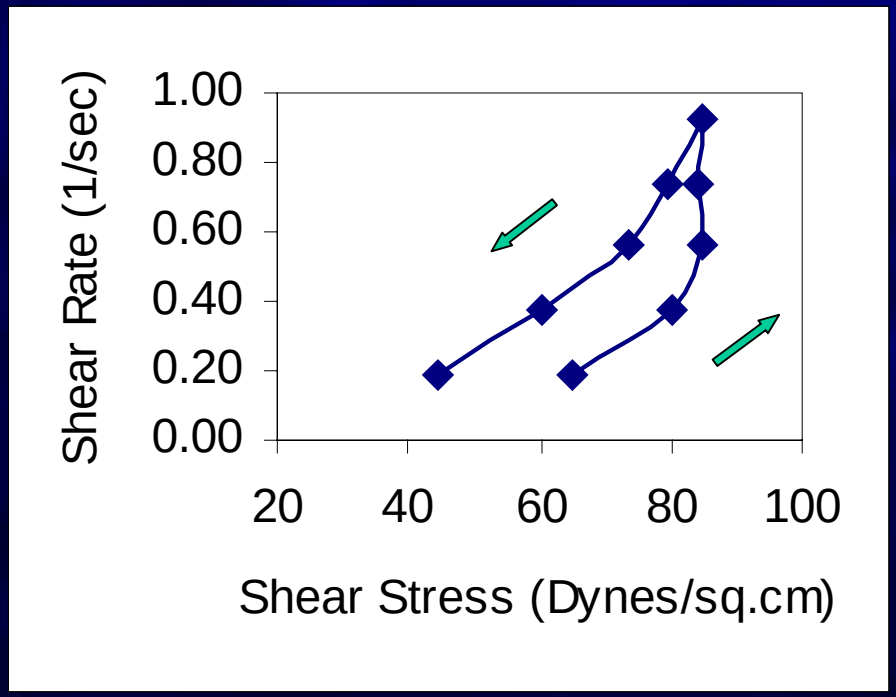

## HPMC



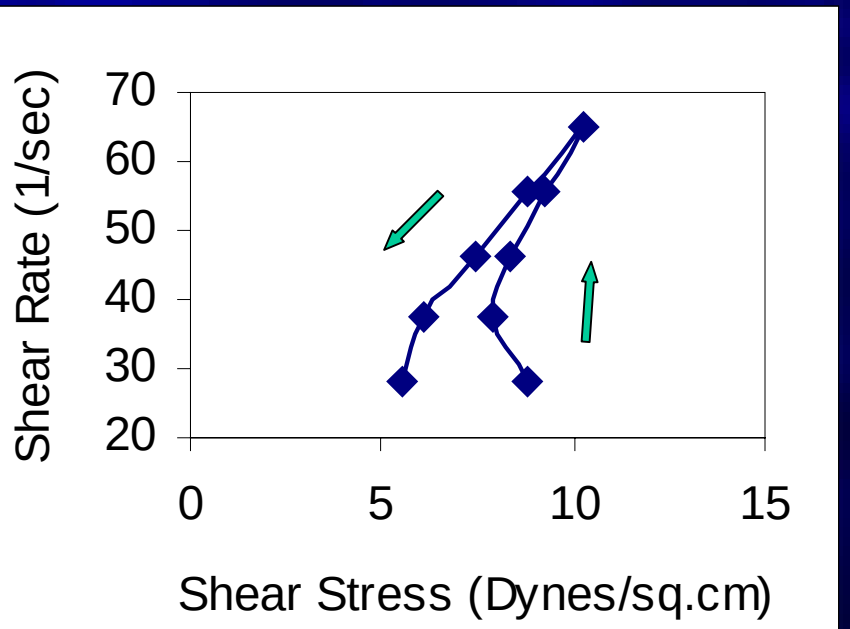

CP = Pseudoplastic, thixotropic,loss of internal structure
HPMC = Pseudoplastic, thixotropic, “Structure recovery”

# Rheology of Tablet Dispersions

## XG




## HPC




XG = Pseudoplastic, thixotropic (at very low shear rates)
HPC = Pseudoplastic, thixotropic

# Bioadhesion Testing

**Principle – Force required to break the adhesive bond between a biological or synthetic membrane and test sample is measured as bioadhesive strength**

- **Equipment – Texture analyzer (Stable Microsystems, UK)**
- **Model membrane – Cellophane soaked for 2 hours**
- **Instrumental parameters**

  **Pre test speed – 0.3 mm/sec**

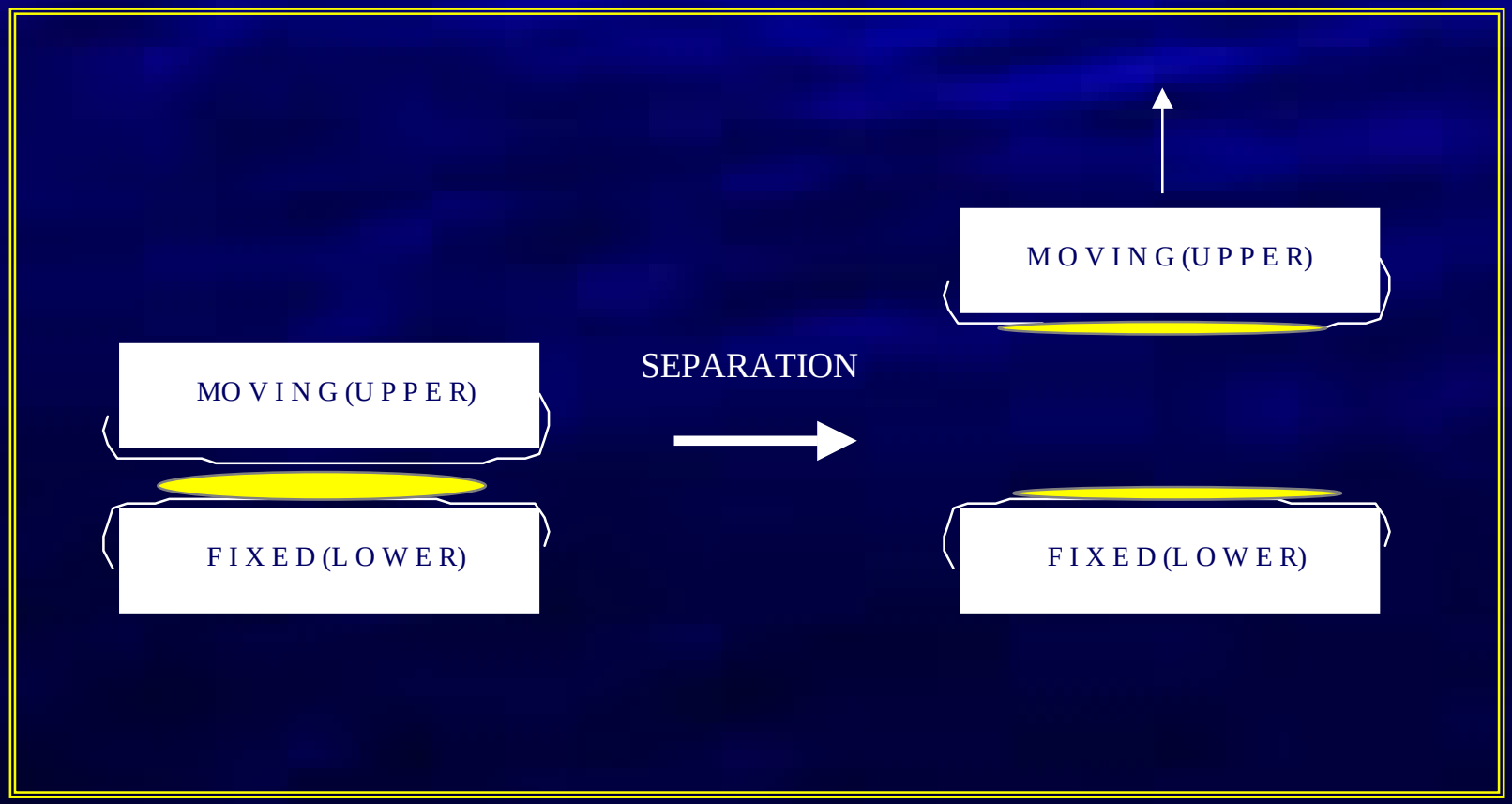
  **Test speed – 0.1mm/sec**

  **Post speed – 0.1 mm/sec**

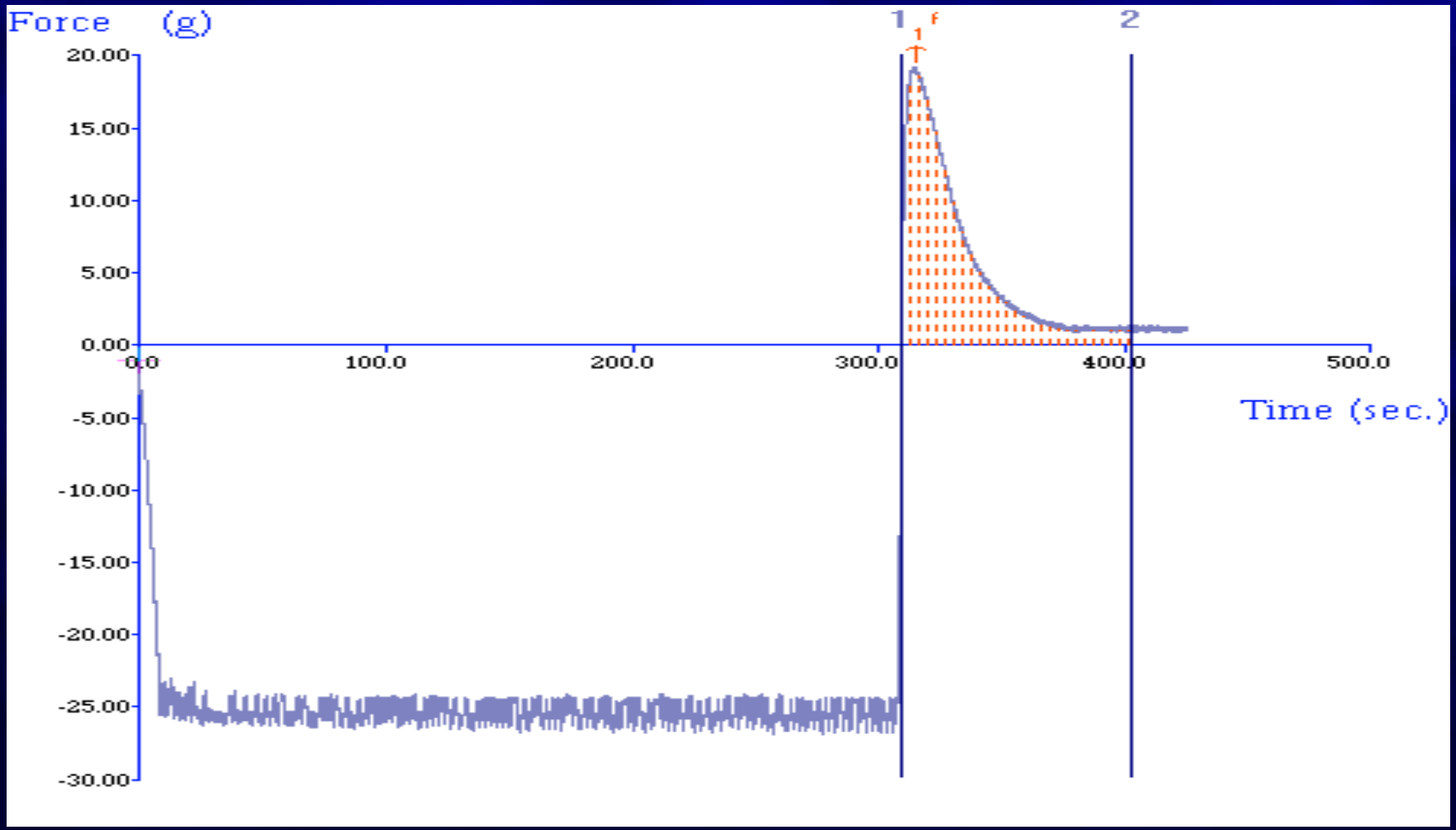
  **Contact time – 5 minutes**

  **Contact force – 0.25 N**

# BIOADHESION TEST ASSEMBLY - Horizontal
## (Mechanism of separation)



# Bioadhesive strength (maximum force) and work of adhesion (area under curve) measured using a texture analyzer (Representative graph)



# Bioadhesion Testing

Unit dose of the formulation was dispersed in 4 ml of saline. Dispersion (0.5 gm) was used for test.

| Polymer / Tests | CP | PC | HPMC | XG | SCMC | HPC |
|---|---|---|---|---|---|---|
| **Work of Adhesion (N.s) ± SD** | 0.83 ± **0.24** | 0.5 ± **0.06** | 3.83 ± **1.23** | 2.95 ± **1.48** | 1.56 ± **0.83** | 2.79 ± **0.39** |
| **Bioadhesive Strength (Dynes/cm$^2$)** | 3332 | 3221 | 5324 | 4857 | 3836 | 4279 |

# Osmolality

Tablet was dispersed in 10 ml of saline, filtered through Whatman paper and 10 µl of the resulting solution was analyzed for osmolality

| Test \ Polymer | CP | PC | HPMC | XG | SCMC | HPC |
|---|---|---|---|---|---|---|
| Osmolality (mmol/Kg) | 341 | 342 | 372 | 373 | 356 | 340 |

# Conclusions

- Hardness
  - **PC and XG** were found to be best among all polymers
- Friability
  - All the formulations conformed to acceptable limits except **SCMC**
- Disintegration Time
  - **HPC and HPMC** gave least disintegration time compared to other polymers

# Conclusions

- pH of dispersions
  - All the formulations gave acidic pH when dispersed in $SVF_M$
- Rheology
  - HPMC – recovery of structure, pseudoplastic system
  - CP & PC – loss of structure
  - HPC – initial shear thinning then usual pseudoplastic behaviour

# Conclusions

- Bioadhesion
  - Tablets containing **HPMC**, **XG**, and **HPC** exhibited better bioadhesion as compared to other formulations
  - HPMC > XG > HPC > SCMC > CP = PC
- Osmolality
  - Both **XG** and **HPMC** gave highest osmolality among polymers studied

# Conclusions

- Therefore, it can be concluded that **HPMC** and **HPC** are the best bioadhesive polymers for vaginal tablets under experimental conditions
- Carbopol and Polycarbophil yielded relatively lower bioadhesion under experimental conditions
- SCMC is not a good bioadhesive polymer for use in vaginal tablets

# Acknowledgements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The views expressed by the authors do not necessarily reflect the views of DBT, CONRAD


Thank you