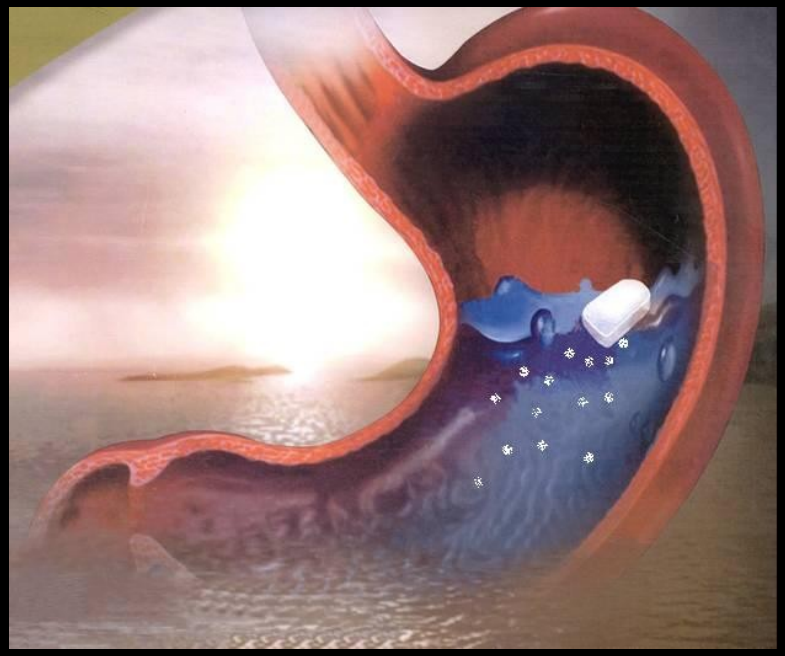
Recent Advances in Formulation & Evaluation Of GRDDS



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- INTRODUCTION to GRRDS
- GRDDS TECHNOLOGIES
- EVALUATION OF GRDDS – In vitro
- EVALUATION OF GRDDS – In vivo

Introduction to GRDDS

Physiological limitations of orally administered drugs:

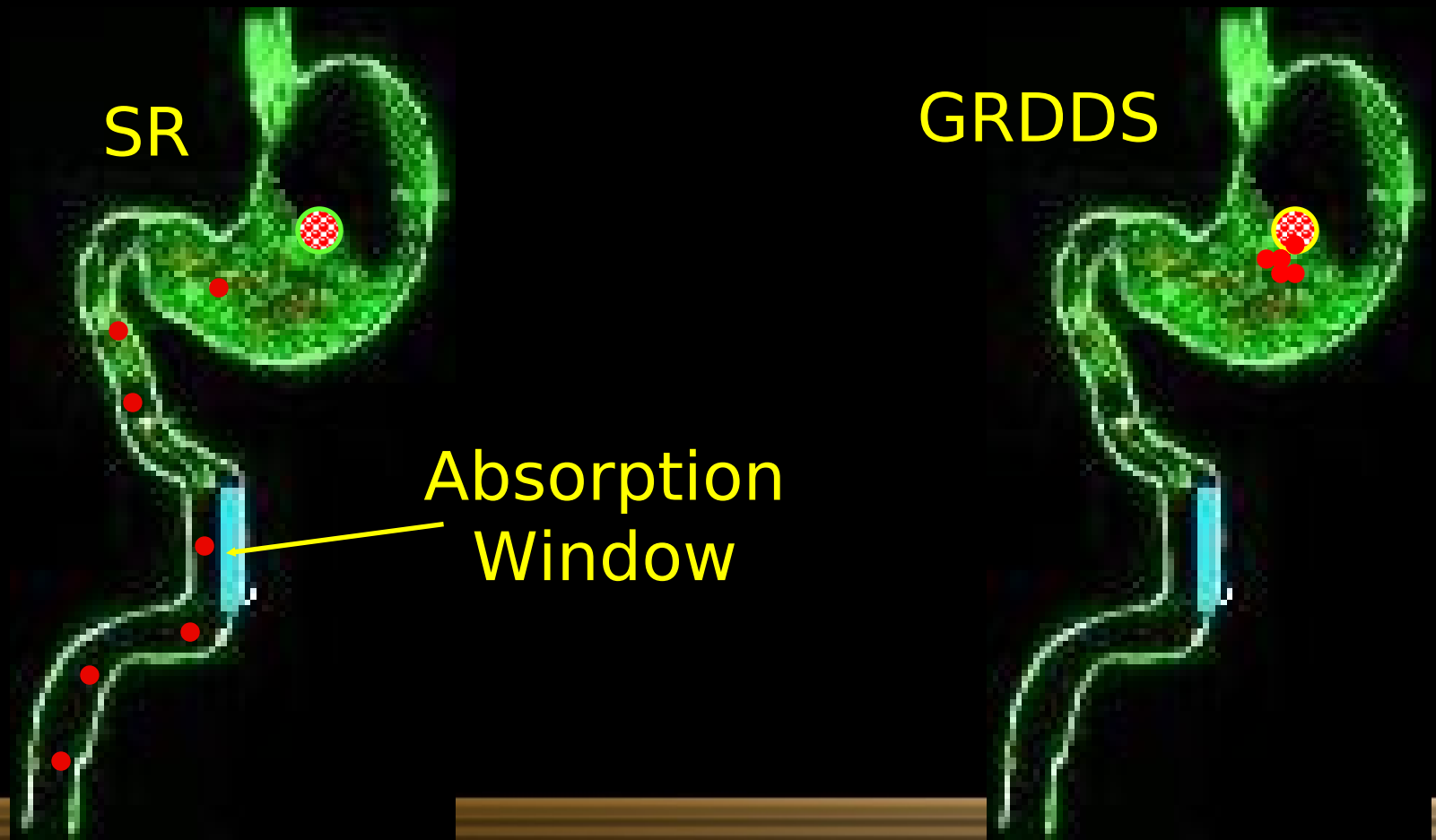
- Variable gastric emptying time (GET)
- Short Gastric residence time (GRT)
- Incomplete drug release due to brief gastrointestinal transit time (8-12 h)

DRUGS WHICH REQUIRE GRDDS

[A] NARROW ABSORPTION WINDOW

Narrow absorption window at upper part of GIT

Levodopa/ Riboflavin



Rationale for GR	Name of drug
• pH-dependant absorption from stomach (acidic drugs)	Furosemide
• Degradation at higher pH (higher stability at lower pH)	Captopril
• Degradation in intestine or colon	Ranitidine
• Higher solubility at lower pH or weakly basic drugs	Cinnarizine / Verapamil
• Drugs for local action	Antacids, anti-ulcers antibacterials for H. pylori

Gastro-Retentive Drug Delivery Systems(GRDDS)

Drug delivery systems that remain for prolonged time in the gastrointestinal tract

Advantages of GRDDS

- Prolongation and control of gastric emptying time
- Drugs present at absorption site for longer time
- Improved bioavailability
- Reduced drug wastage

Limitations of GRDDS

- Fed and Fasted States
- Intake of type of meal
- High level of fluids in stomach
- Unsuitable for drugs absorbed along entire GI tract e.g. nifedipine
- Drugs irritant to the gastric mucosa

GI characteristics in humans

- Volume of stomach
- Gastric pH in fasting state
- Duodenal diameter
- Small intestinal transit time
- Total git transit time
- Size which does not empty from stomach

- 1500 ml
- 2
- 3-4 cm
- 180+60min
- 20-30 h
- Longer than 5 or larger than 3 cm

GRDDS TECHNOLOGIES

[A] Low Density Approach

[B] Expandable Approach

[C] Bio/Muco-adhesive Approach

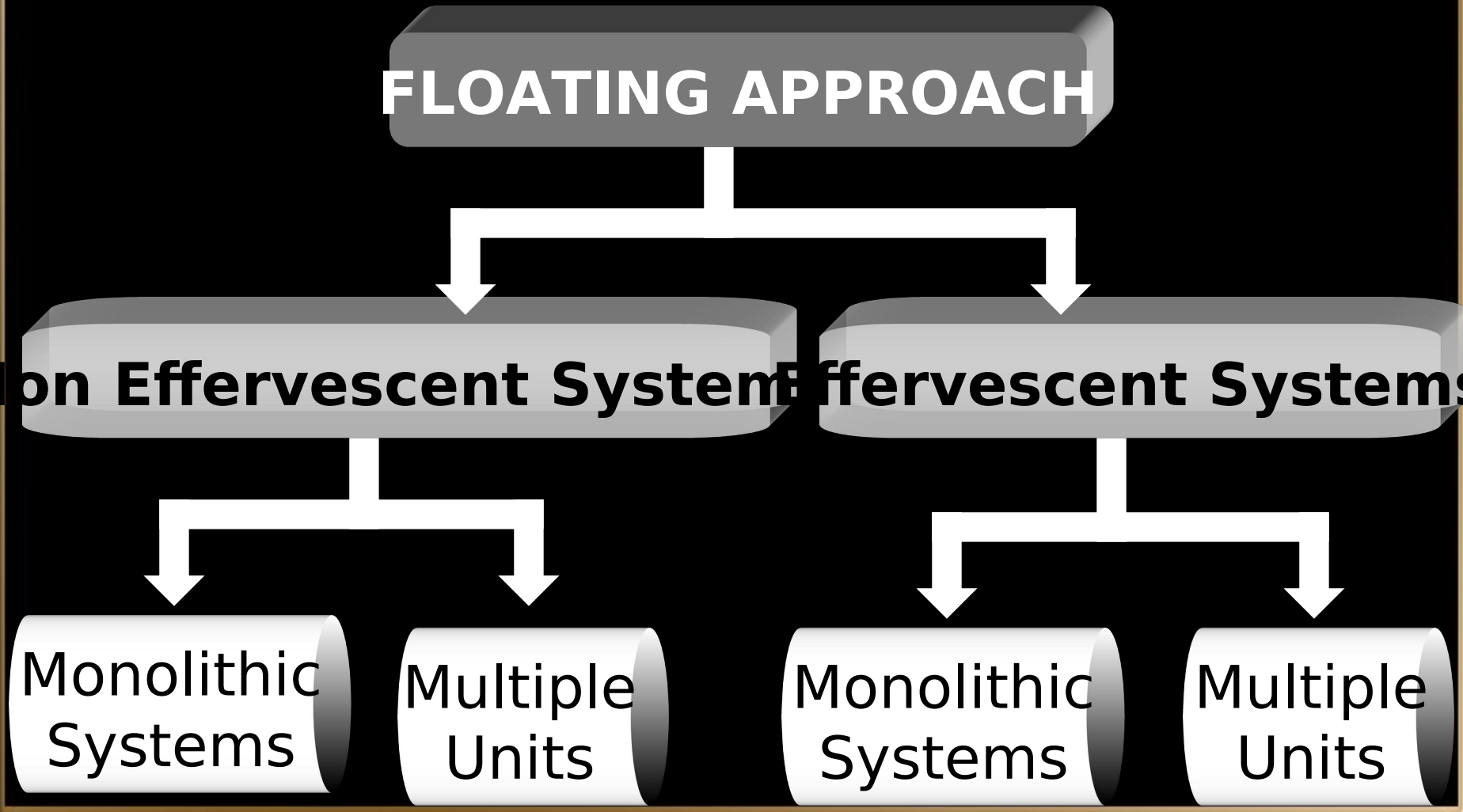
[D] High Density Approach

Floating Systems/Low-Density Systems/Hydrodynamically Balanced Systems

- Bulk Density of dosage forms lower than gastric fluids, remain floating in gastric fluid
- Controlled Release of drug from the system
- Increase in gastric retention time

GRDDS TECHNOLOGIES

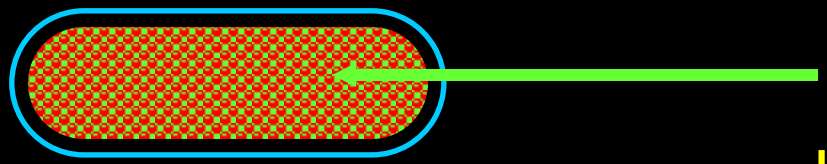
[A] LOW DENSITY APPROACH



A.1 – FLOATING – NON EFFERVESCENT

MONOLITHIC SYSTEMS

HBS™ CAPSULE



DRUG

+

Highly Swellable Gel forming Hydrocolloids

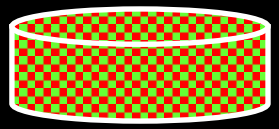
- HPMC
- HPC
- HEC
- MC

A.1 – FLOATING – NON EFFERVESCENT

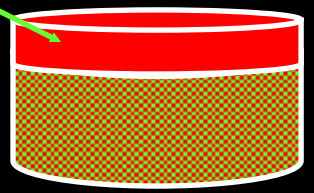
MONOLITHIC SYSTEMS

MATRIX TABLET

Single Layer Tablet



Bilayer Tablet

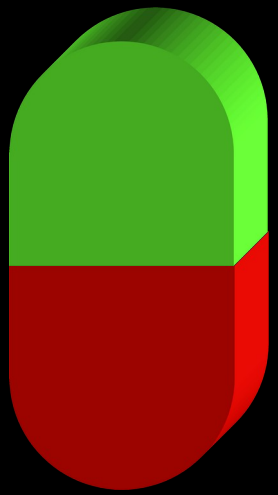


A.1 – FLOATING – NON EFFERVESCENT

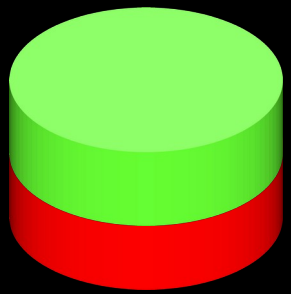
MONOLITHIC SYSTEMS

NON MATRIX BILAYER SYSTEM

BILAYER CAPSULE



BILAYER TABLET



A.1 – FLOATING – NON EFFERVESCENT

MONOLITHIC SYSTEMS

TABLET with FOAM

- Polypropylene Foam
- Hydrophobic Powder
- Open-cell Structure
- Highly Porous
- Low Inherent Density

TABLET with LIPID

Glyceryl Monooleate

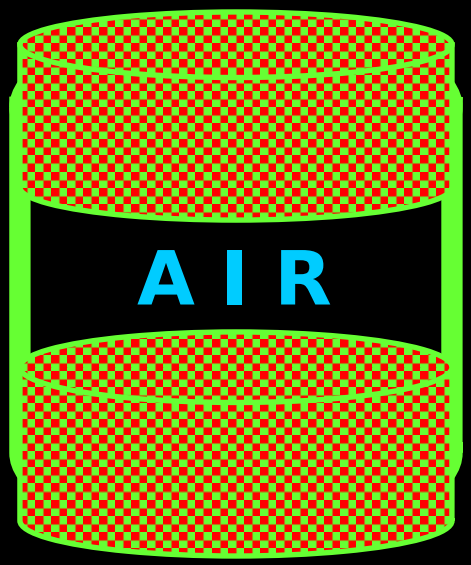
- Swells in Water
- Converted to Liquid Crystals - Cubic Shape

Melted And Molded

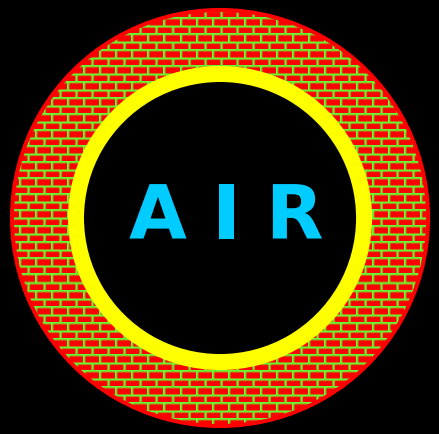
A.1 – FLOATING – NON EFFERVESCENT

MONOLITHIC SYSTEMS

TABLETS IN CYLINDER



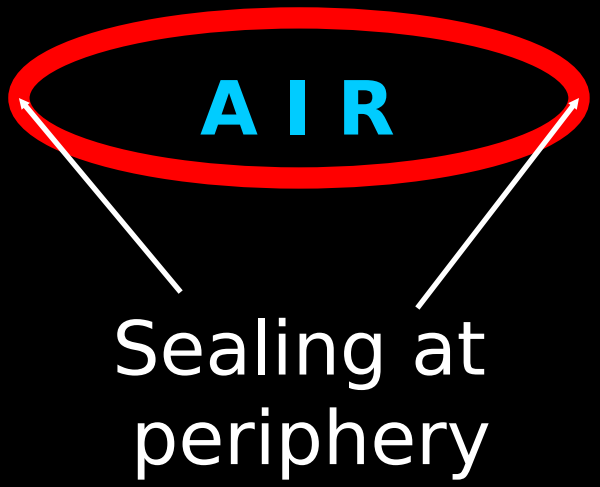
COATED HOLLOW GLOBULAR SHELL



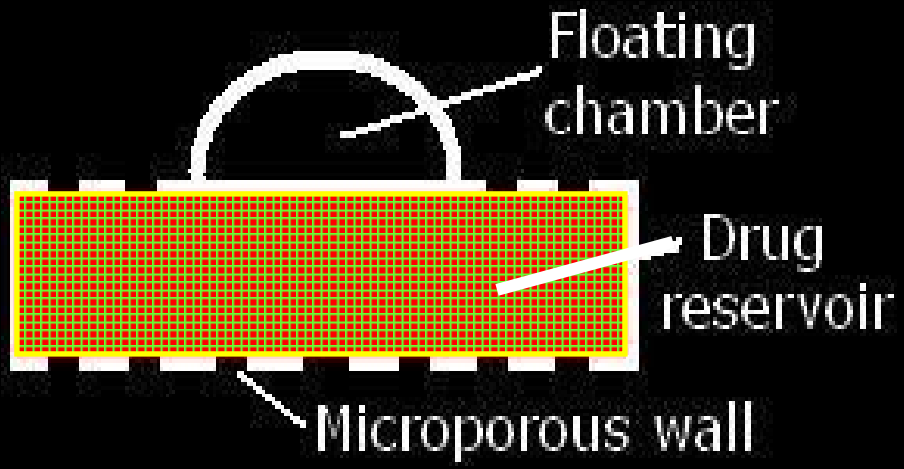
A.1 – FLOATING – NON EFFERVESCENT

MONOLITHIC SYSTEMS

MULTILAYER FILM



MICROPOROUS RESERVIOR

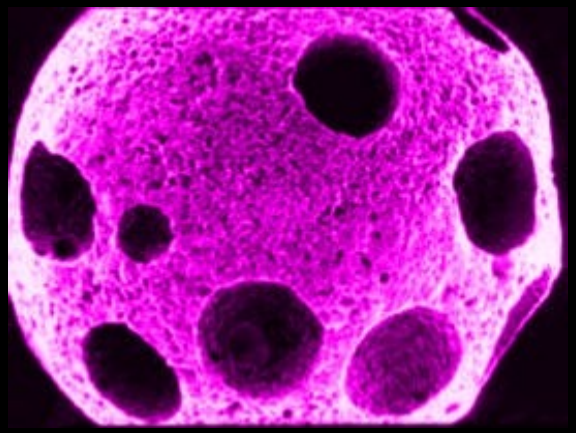


A.1 – FLOATING – NON EFFERVESCENT

MULTIPLE UNITS

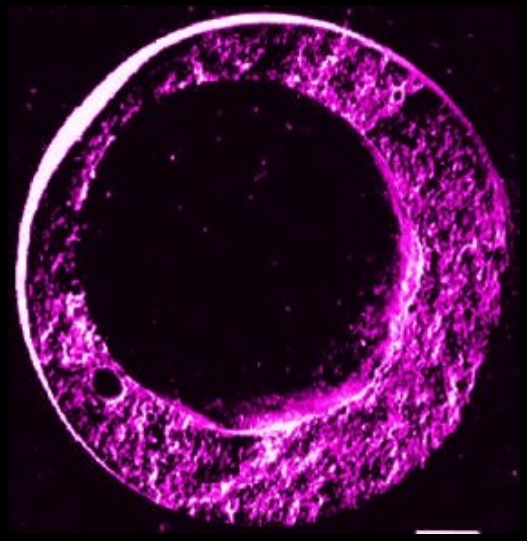
HOLLOW MICROSPHERE

Solvent Evaporation



MICROBALLOON

Emulsion Solvent Diffusion Method



A.1 – FLOATING – NON EFFERVESCENT

MULTIPLE UNITS

FOAM Containing MICROPARTICLES

Drug,
Polymer

Dissolved

Organic
Solvent

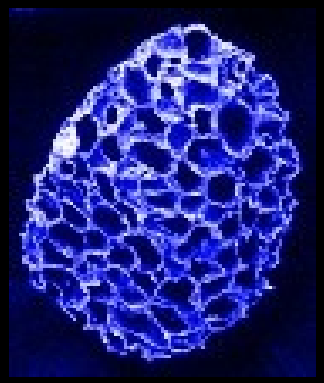
Add
to

Aqueous
PVA
Solution

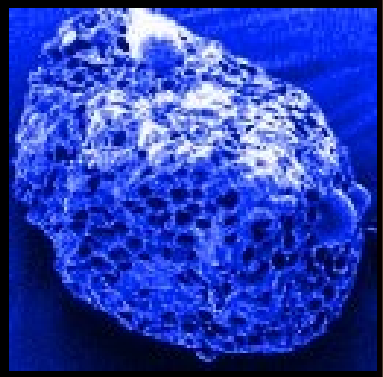
Dispersed

FOAM

Solvent Evaporation Method



Only
FOAM



FOAM
Microparticle

A.1 – FLOATING – NON EFFERVESCENT

MULTIPLE UNITS

CALCIUM SILICATE As FLOATING CARRIER

- Highly Porous
- Large Pore Volume
- Low Inherent Density
- Granules Drug
  HPMC
  Ca-Silicate

GELUCIRE® GRANULES

- Hydrophobic Lipid
- Diff. Grades – 39/01
  43/01
- Low Inherent Density
- Melt Granulation
- SR of Highly Soluble Dru

A.2 – FLOATING – EFFERVESCENT

MONOLITHIC SYSTEM

MATRIX TABLET

- Bicarbonate + Polymer
- Single Layer Tablet
- Bilayer Tablet
- Triple Layer Tablet

MATRIX TABLET with CARBOPOL

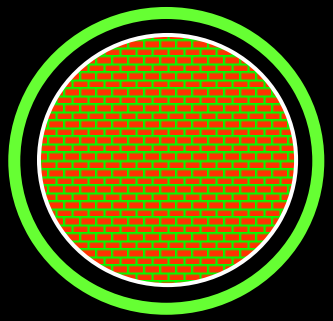
- pH dependent Gelling
- Only Carbopol
  - NO GELLING
- Bicarbonate + Carbopol
  - GELLING due to Alkaline

MICROENVIRONMENT

A.2 – FLOATING – EFFERVESCENT

MONOLITHIC SYSTEM

COATED EFFERVESCENT CORE

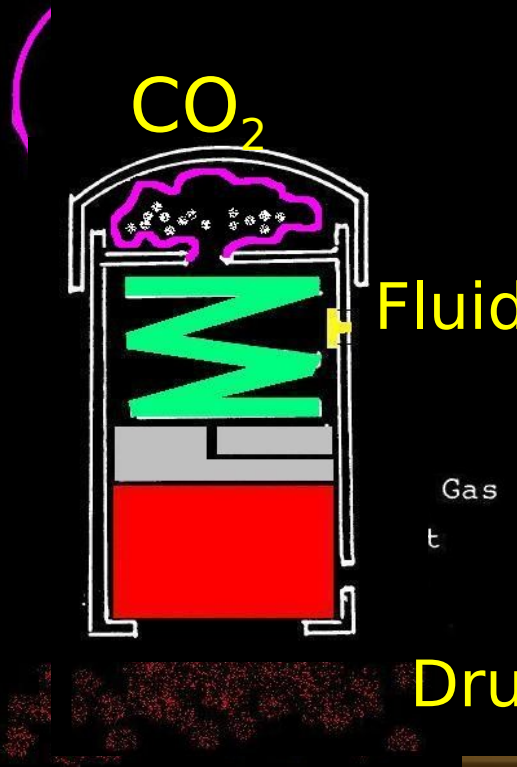


MULTIPLE FILM

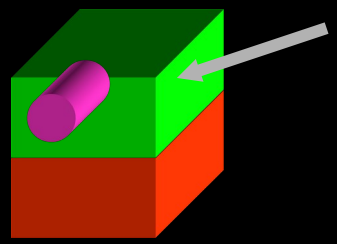
A.2 – FLOATING – EFFERVESCENT

MONOLITHIC SYSTEM

PROGRAMMABLE DRUG DELIVERY



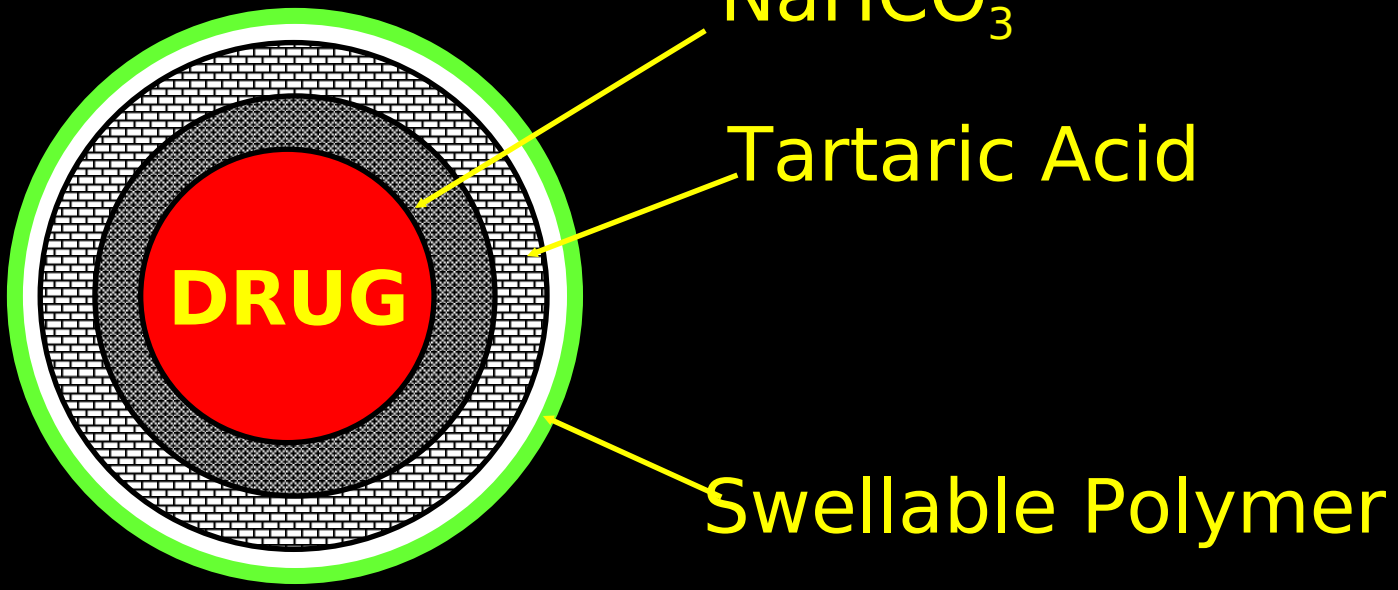
SYSTEM with INFLATABLE CHAMBER



A.2 – FLOATING – EFFERVESCENT

MULTIPLE UNITS

FLOATING PILLS



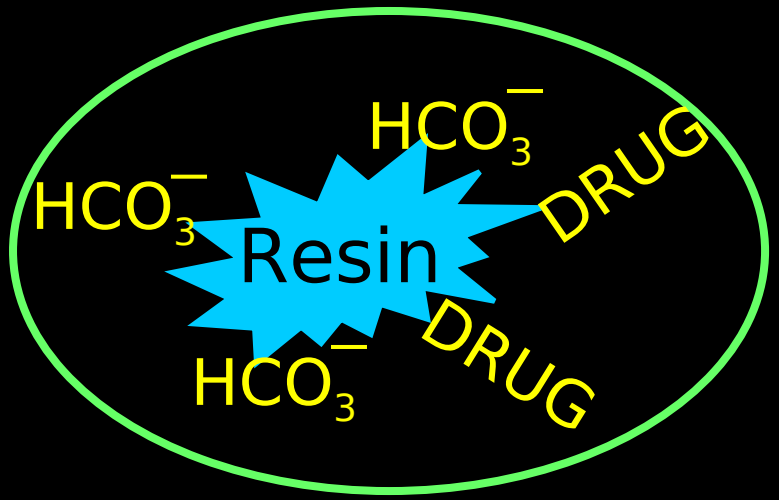
A.2 – FLOATING – EFFERVESCENT

MULTIPLE UNITS

ION EXCHANGE RESIN BEADS

$H^+ Cl^-$

$H^+ Cl^-$



$H^+ Cl^-$

$H^+ Cl^-$

$H^+ Cl^-$

Uncoated Beads – No Floating – Escape of CO_2

GRDDS TECHNOLOGIES

[B] EXPANDABLE APPROACH

- After ingestion they swell to an extent that their exit is prevented from the stomach.
- Dosage form retained for prolonged time due to Retropulsion
- PLUG TYPE devices

GRDDS TECHNOLOGIES

[B] EXPANDABLE APPROACH

EXPANDABLE APPROACH

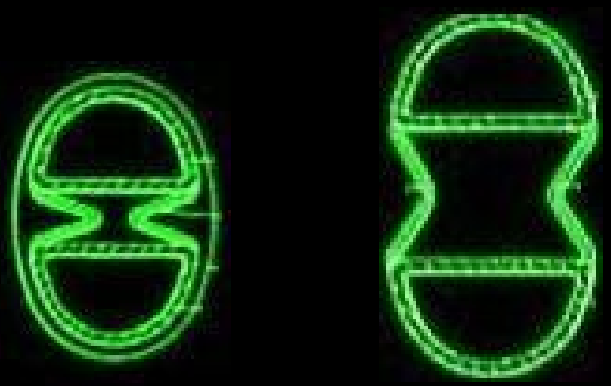
- **Swelling Systems**
- **Unfolding Systems**

SHAPE MEMORY

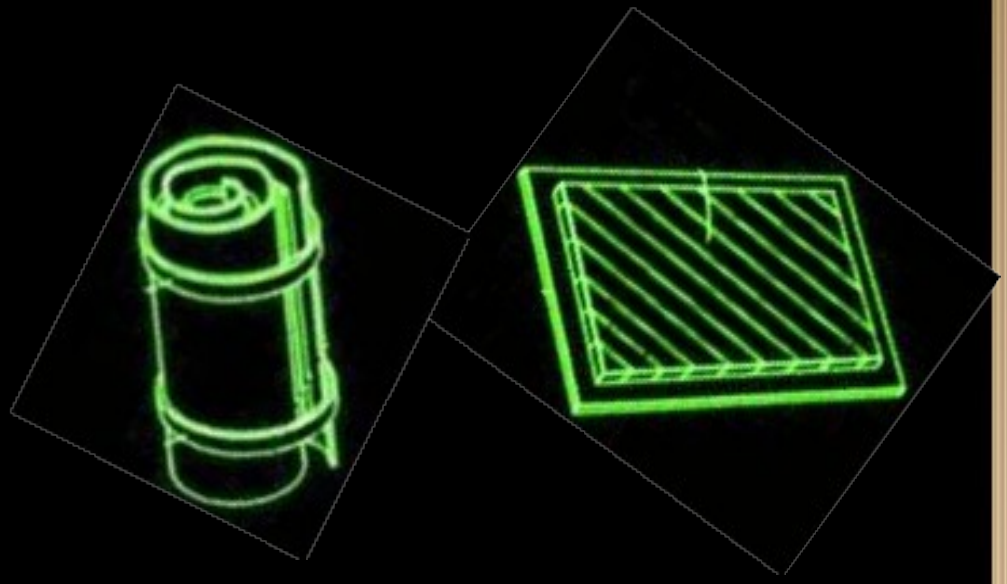
[B] – EXPANDABLE APPROACH

B.2 – UNFOLDING SYSTEMS

OBSTRUCTING MEANS



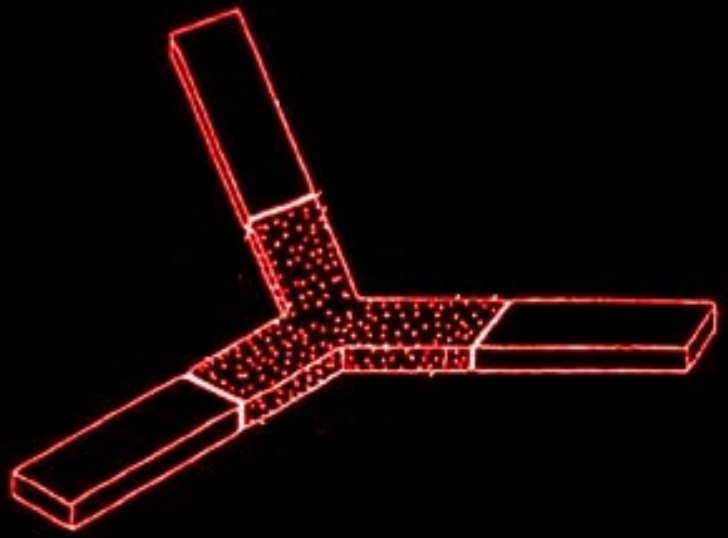
MULTILAYER FILMS



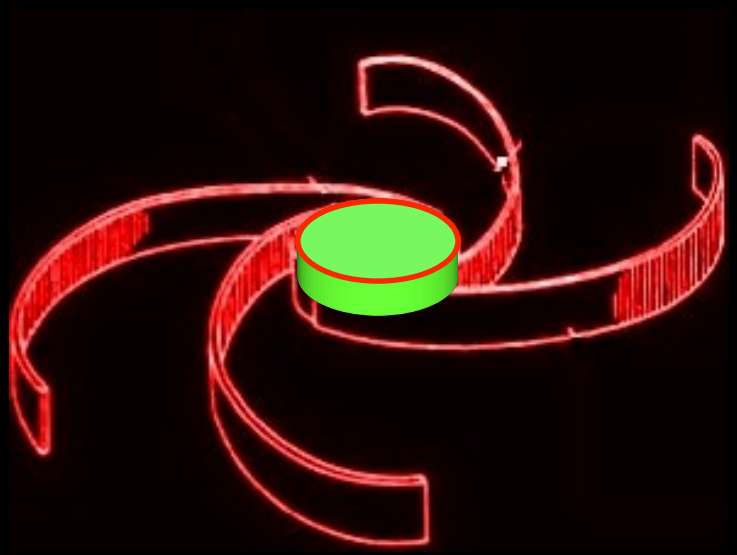
[B] – EXPANDABLE APPROACH

B.2 – UNFOLDING SYSTEMS

GEOMETRIC CONFIGURATIONS



RECEPTACLE MEANS



Bioadhesive Systems

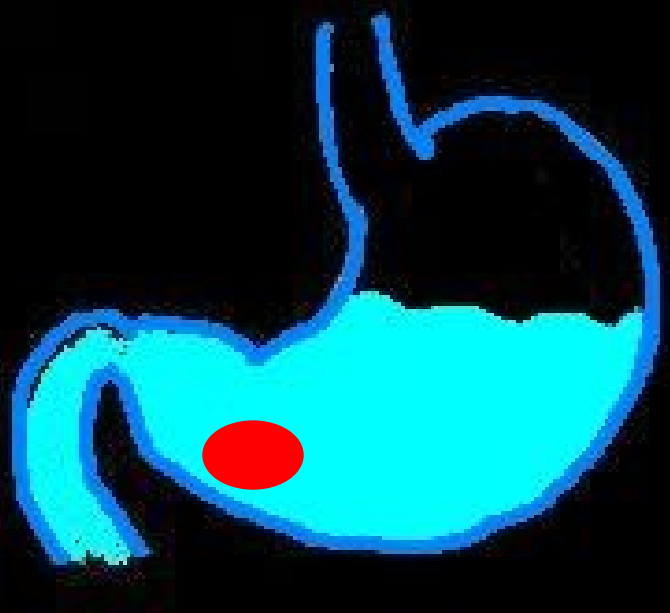
- Localize the dosage form within the stomach by using principle of bioadhesion
- Use of bioadhesive polymers that adhere to the epithelial surface of git
- Prolonged drug release and increased gastric retention

GRDDS TECHNOLOGIES

[C] BIO/MUCO ADHESIVE APPROACH

High Density Systems

- Dosage forms coated with inert heavy metals such as ZnO_2/$BaSO_4$ having density greater than stomach contents (~ 1.004 g/cm2)



EVALUATION OF GRDDS

IN VITRO

FLOATING DOSAGE FORMS

Floating Lag Time

- In 0.1 N HCl or Simulated Gastric Fluid
- Important for Effervescent Systems – For reaction
- Negligible for non-effervescent of hollow microspheres/ microballons
- Housekeeper waves of the stomach may sweep out the dosage form.

Specific Gravity / Density

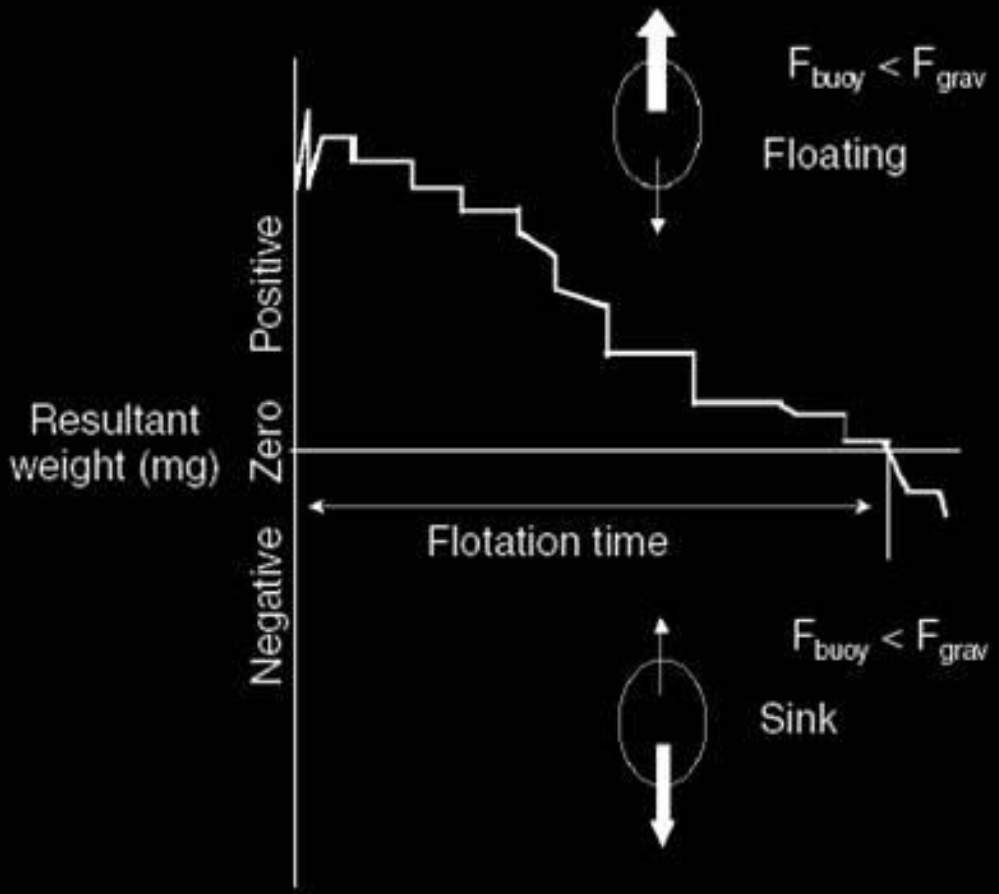
- Important to predict floatibility
  - Ratio of tablet weight to tablet volume (height & diameter)
  - For multiple units – mass volume of known mass weight

Floating Time / Buoyancy Time

- Total time period between placing a dosage form in the medium to the time it remains floating
- Indicates duration of GR
- For multiple units, Fraction of microspheres settled down as a function of time by determining its weight on drying

Resultant Weight

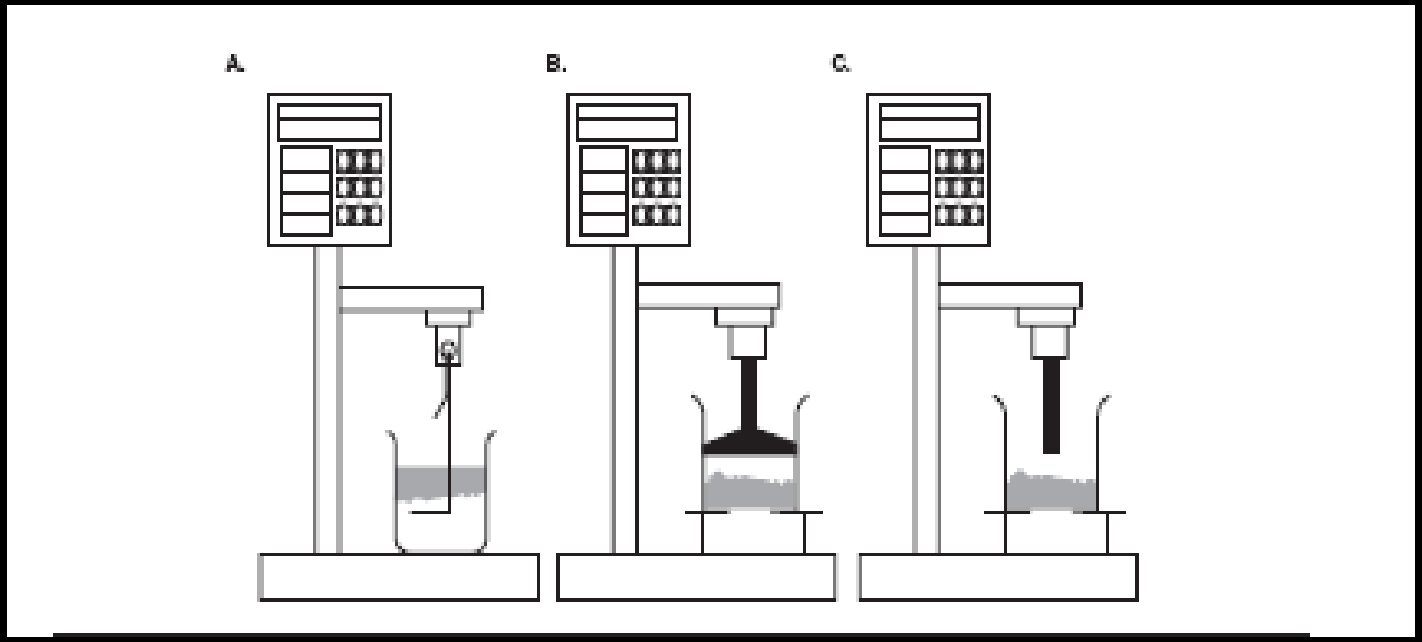
- Total time period between placing a dosage form in the medium to the time it remains floating
- Indicates duration of GR



Raft Characterization

- Raft Strength

- Raft Resistance to Reflux



Reproduced from : A review by
Parikh & Amin in **Expert Opinion On Drug Delivery (2008), 5(9), 1-15**

EVALUATION OF GRDDS

IN VITRO EVALUATION

SWELLING SYSTEM

Swelling Index / Water Uptake / Weight Gain

Swelling Capacity of the polymer in contact with the dissolution medium

$$WU = (Wt - Wo) * 100 / Wo$$

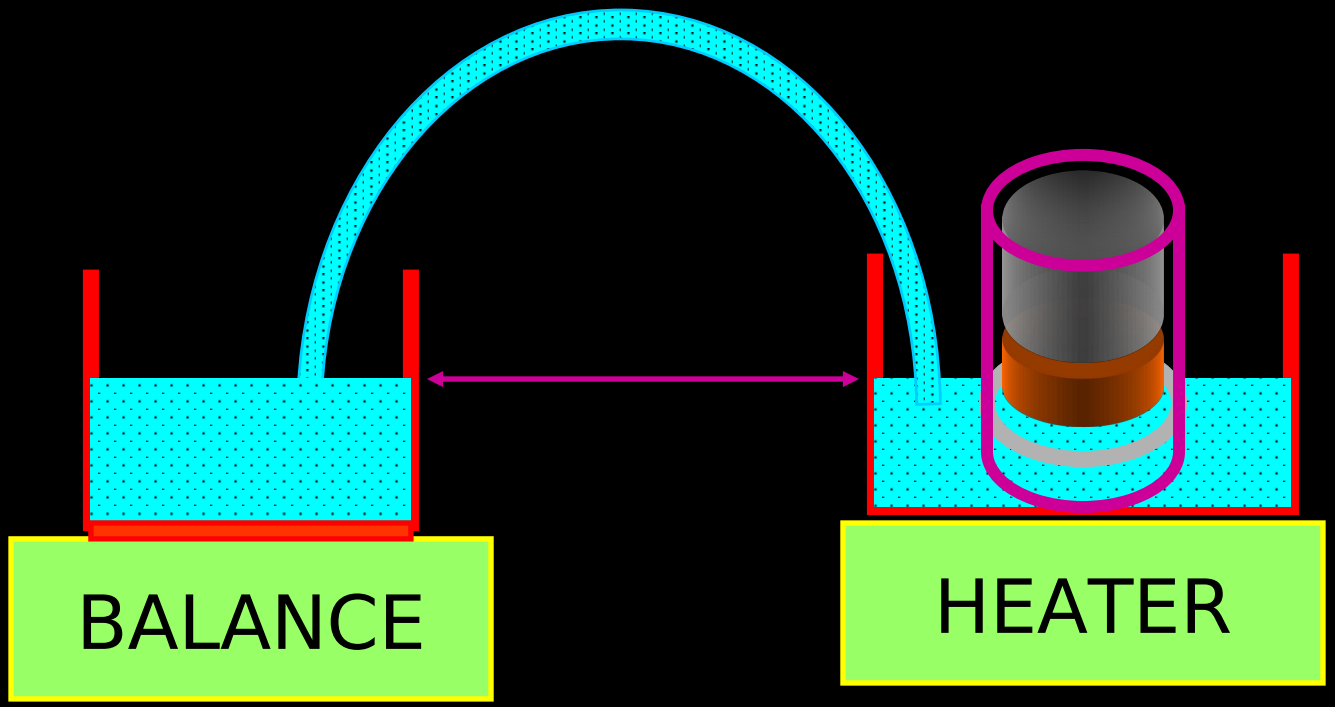
Important for GRDDS based on Swelling approach.

Also indicative of release properties

EVALUATION OF GRDDS

IN VITRO EVALUATION

SWELLING SYSTEM



EVALUATION OF GRDDS

IN VITRO EVALUATION

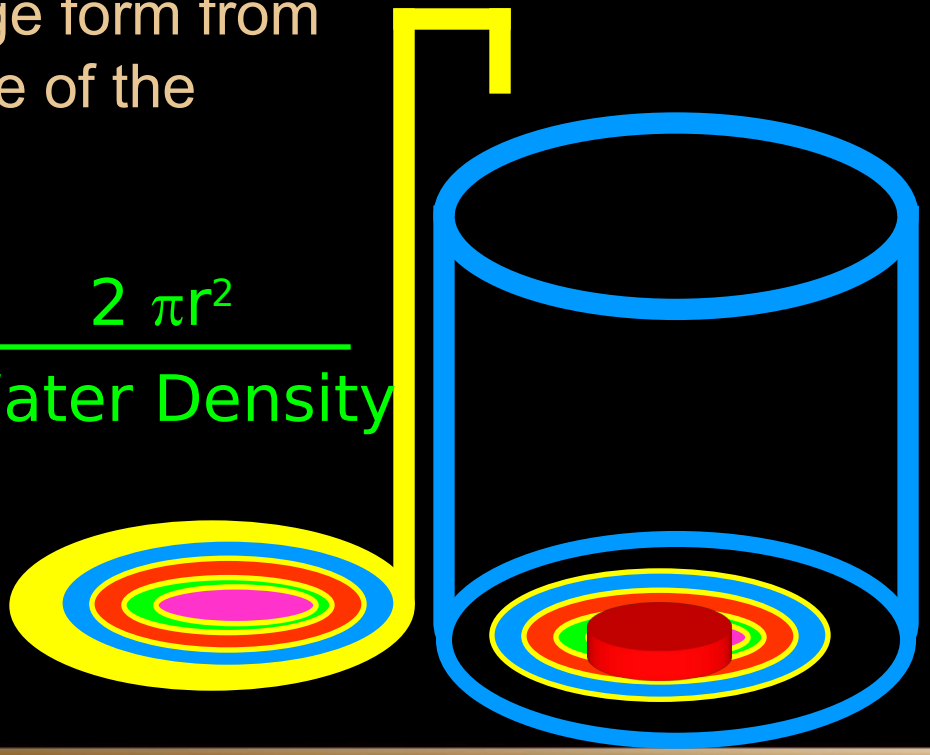
Penetration Rate

Water uptake test for Swellable dosage forms

Requires removal of dosage form from the media. Leads to rupture of the matrix

$$PR = \frac{\text{Water Uptake}}{\text{Per Unit Time}} \times \frac{2\pi r^2}{\text{Water Density}}$$

New method: Weight determination at regular time intervals



Exposed Size Parameter

Test specifically for unfolding type of systems.

Placed in a capsule.

Suspended in dissolution medium

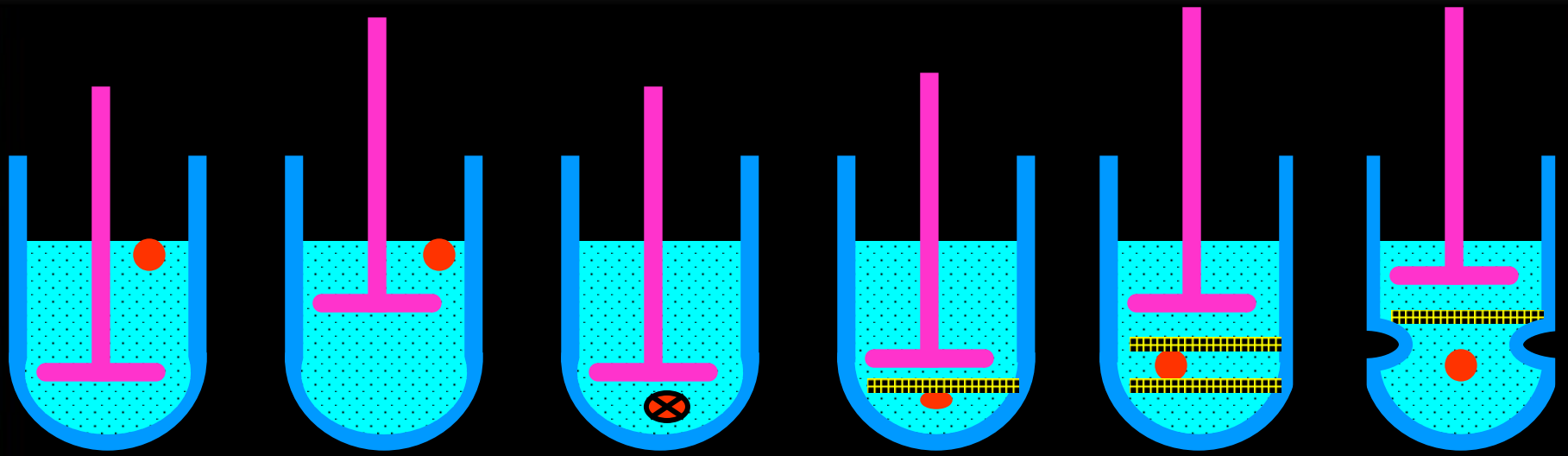
Unfolding Capacity ascertained

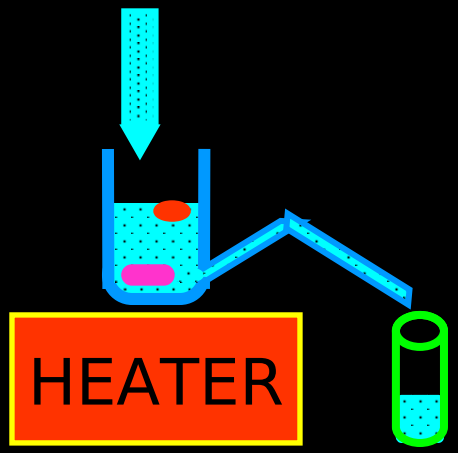
In-vitro Drug Release

- Release Profile in SGF / 0.1 N HCl
- Use of USP Dissolution Apparatus I or II
- Use of Enzymes and surfactants required
- Position of Floating Type very Critical
  - Use of Sinkers

EVALUATION OF GRDDS

IN VITRO DISSOLUTION





Modified Rossett-Rice Test

EVALUATION OF GRDDS

1. Roentgenography **IN VIVO**
2. γ-SCINTIGRAPHY
3. GASTROSCOPY
4. MAGNETIC MARKER MONITORING
5. ULTRASONOGRAPHY
6. ^{13}C OCTANOIC ACID BREATH TEST

Platform technologies for GRDDS

Company	Platform technology	Type of technology
Depomed	AcuForm	Polymer-based technology
Intec	Accordion Pill	Expandable film, filled in capsule
Sun	Gastro Retentive	Coated multilayer
Pharma	Innovative Device	floating and swelling system

- Merrion Pharma — GI Retention System (GIRES) — Gas generating inflatable pouch in capsule
- FlamelMicropump — Gastro-retention with osmotic system
- Roche Hydrodynamically Balanced System — Matrix forming polymer-based floating system

MARKETED PRODUCTS

Brand Name	Drug (dose)	Company
Madopar®	Levodopa (100 mg), Benserazide (25 mg)	Roche, USA
Valrelease®	Diazepam (15 mg)	Hoffman LaRoche, USA
Liquid Gaviscon®	$Al(OH)_3$ + $MgCO_3$	GlaxoSmithKlein, India
Topalkan® Liquid	Al – Mg antacid	Pierre Fabre Drug, France
Almagate Flotcoat®	Al – Mg antacid	
Conviron®	Ferrous sulfate	Ranbaxy, India
Cifran OD®	Ciprofloxacin (1 g)	Ranbaxy, India
Cytotec®	Misoprostal (100/200 μg)	Pharmacia, USA