

Preparation of hollow microspere loaded with Anti-Infective drug (Cefexime)

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Abstract- In the present study an attempt was made to prepare Hollow Microspheres loaded with an Anti-Infective Drug. Cefixime is a third- generation cephalosporin antibiotic which is highly effective against various infections. Different formulations were prepared by Emulsion Solvent Diffusion method. FTIR and DSC studies confirmed that there was no interaction between drug and the polymers. Particle size for all formulations were within the range of 560-570 nm respectively. The images from SEM revealed that the particles were spherical in shape. The drug entrapment efficiency of formulations was found to be in the range of 89.34%. Thus, the prepared Hollow Microspheres proved to maintain the therapeutic index over a continued period of time and be a potential candidate as a sustained drug delivery system.

Keywords: Cefixime, Hollow Microspheres, Sustained Drug Delivery, Invitro drug release, Pharmacokinetics.

I. INTRODUCTION:

The most helpful and commonly utilized course of medicate conveyance has been by verbal ingestion. Cefixime can be effortlessly retained from the GIT and having a brief half-life are disposed of rapidly from the blood circulation. To maintain a strategic distance from these issues, gastro-retentive dose frame is defined which offer assistance drag out the home time of the medicate in the stomach and make strides their bioavailability.

The most helpful and commonly utilized course of sedate conveyance has generally been by verbal ingestion. This can be mostly due to the ease of organization as well as the truth that the gastrointestinal [GI] physiology offers more adaptability in dose frame than more other routes.

Drugs that are effortlessly retained from the GIT and having a brief half-life are disposed of rapidly from the blood circulation. To maintain a strategic distance from these issues, the verbal controlled sedate concentration in the serum remains for longer period of time. Be that as it may, fragmented discharge of the sedate and a shorter home time of measurement shapes in the upper gastrointestinal tract, a unmistakable location for assimilation of numerous drugs, will lead to lower bioavailability. In this way, gastroretentive dose shapes, which draw out the home time of the drugs in the stomach and make strides their bioavailability, have been developed.

Approaches to Gastric Retention:

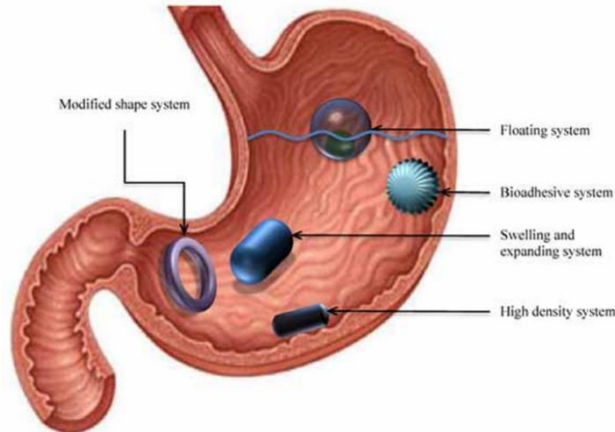
A number of approaches have been utilized to increment gastric maintenance time [GRT] of a dose frame in stomach by utilizing a assortment of concepts. They are: 7,8

1. Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk thickness lower than gastric liquids and in this way, stay buoyant in stomach for a delayed period of time, without influencing the gastric purging rate. Whereas the framework coasts on gastric substance, the sedate is discharged gradually at a wanted rate from the framework. After the discharge of medicate, the remaining framework is purged from the stomach. This comes about in an increment in gastric maintenance time and a superior control of variances in plasma sedate concentrations. Coasting frameworks can be classified into two unmistakable categories, non-effervescent and bubbling systems.

2. Tall thickness systems:

These frameworks with a thickness of around 3 g/cm³ are held in the rugae of stomach and are able of withstanding its peristaltic developments. A thickness of 2.6- 2.8 g/cm³ acts as a limit esteem after which such frameworks can be held in the lower parts of the stomach. High-density definitions incorporate coated pellets. Coating is done by overwhelming inactive fabric such as barium sulphate, zinc oxide, titanium dioxide, press powder etc.

Figure 1: Approaches to gastric retention**3. Osmotic directed systems:**

It is comprised of an osmotic pressure-controlled medicate conveyance gadget and an inflatable coating bolster in a bio-erodible capsule. In the stomach the capsule rapidly crumbles to discharge the intragastric osmotically controlled medicate conveyance gadget. The inflatable bolster interior shapes a deformable empty polymeric pack that contains a fluid that gasifies at body temperature to expand the sack. The osmotic controlled medicate conveyance gadget comprises of two components – sedate supply compartment and osmotically dynamic compartment.

4. Particle trade resins:

Ion trade tars are stacked with bicarbonate and a adversely charged sedate is bound to the gum. The resultant dots are at that point typified in a semi-permeable layer to overcome the quick misfortune of carbon dioxide. Upon entry in the acidic environment of the stomach, an trade of chloride and bicarbonate particles take put. As a result of this response carbon dioxide is discharged and caught in the layer in this manner carrying globules towards the beat of gastric substance and creating a drifting layer of gum dots in differentiate to the uncoated dots, which will sink quickly.

Types of floating medicine delivery systems:

Floating Drug Delivery Systems (FDDS) can be divided in to two systems.

1. Effervescent system

Effervescent systems include the use of gas generating agents, carbonates (eg. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the expression to produce carbon dioxide(CO₂) gas, therefore reducing the viscosity of the system and making it float on the gastric fluid. These bouncy systems further classified into two types.

1. Gas generating systems.
2. Volatile Liquid/ Vacuum Containing Systems

2. Non- effervescent systems

The Non bouncy FDDS is grounded on medium of, swelling of a polymer or bioadhesion to mucosal subcaste in GI tract. The most generally used excipients in non-bouncy FDDS are gel forming or largely swellable cellulose type hydrocolloids, polysaccharides and matrix forming material similar as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer similar as chitosan and carbopol. The colorful types of this system are as

- i) Single layer floating tablets
- ii) Bilayer floating tablets

3. Alginate beads

Multi-unit floating lozenge forms were developed from snap- dried calcium alginate. globular globules of roughly 2.5 mm periphery can be prepared by dropping a sodium alginate result into waterless result of calcium chloride, causing rush of calcium alginate leading to conformation of pervious system, which can maintain a floating force for over 12 hours. These floating globules gave a prolonged hearthstone time of further than 5.5 hour.

4. Hollow microspheres

Hollow microspheres are considered as one of the most promising buoyant systems, as they retain the unique advantages of multiple unit systems as well as better floating parcels, because of central Hollow space inside the microsphere.

Advantages of floating microspheres:

The advantages of floating microspheres are:

- 1) Enhanced bioavailability.
- 2) Enhanced first pass biotransformation.
- 3) Reduced frequency of dosing.
- 4) Reduced oscillations of medicine attention.
- 5) Inflexibility in lozenge form design.
- 6) Minimized adverse exertion at the colon.

Disadvantages of floating microspheres:

The disadvantages of floating microspheres are:

- 1) Not suitable for medicines that have solubility or stability problem in GIT.
- 2) Medicines which are irritant to gastric mucosa aren't suitable.
- 3) These systems bear a high position of fluid in the stomach for medicine delivery to float and work efficiently.
- 4) These systems aren't profitable over the conventional lozenge forms for those medicines, which are absorbed throughout the gastrointestinal tract.

Mechanism of floating medicine delivery:

When microspheres come in contact with gastric fluids, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel hedge that controls the rate of fluid penetration into the device and consequent medicine release. As the surface face of the lozenge form dissolves, the gel subcaste is maintained by the hydration of the continuous hydrocolloid subcaste. The air trapped by the blown polymer lowers the viscosity and confers buoyancy to the microspheres. Still, a minimum gastric content is demanded to allow proper achievement of buoyancy.

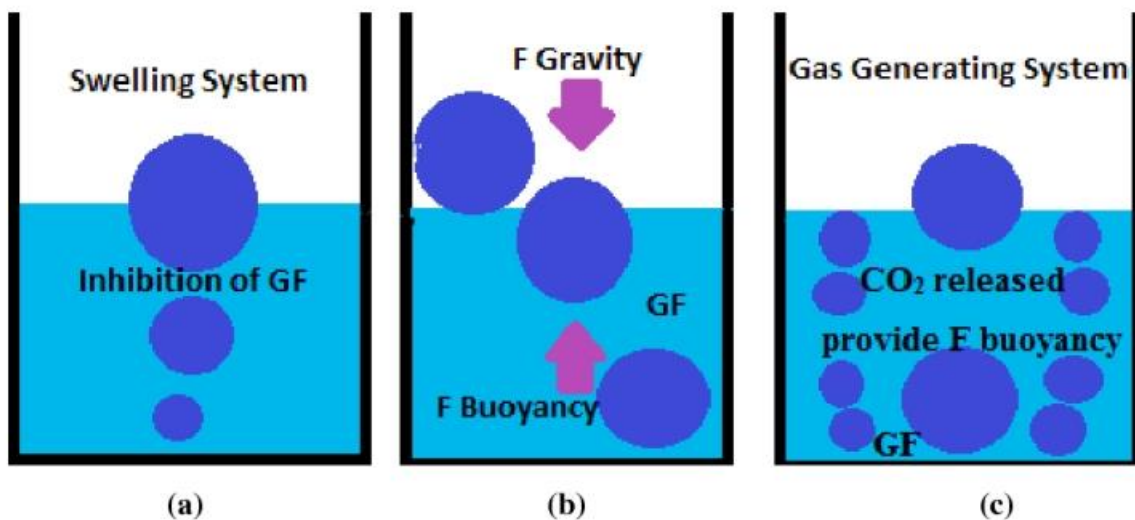


Figure 2: Mechanism of floating drug delivery system

HOLLOW MICROSPHERES

Hollow microspheres are gastroretentive medicine delivery systems grounded on a non-effervescent approach. They're globular empty patches without core. They retain the unique advantages of multiple unit systems and their center hollow space imparts good floating parcels making them promising buoyant systems. These microspheres are free flowing, low viscosity formulations, having a size lower than 200µm, comprising of either proteins or synthetic polymer. The sustained release of medicine from the buoyant systems improves the gastric retention and reduces the oscillations in tube medicine attention. These microspheres were nominated as microballoons due to their characteristic internal hollow structures and excellent floatability in vitro. Medium of depression conformation inside the microspheres. A polymer result in organic detergent is poured in to an agitated waterless result. The organic detergent fleetly partitions in to the external waterless phase and the polymer precipitates around the organic detergent. The posterior evaporation of the entrapped organic detergent leads to the conformation of internal depressions within the microspheres.

Mechanism of cavity formation inside the microspheres

A polymer solution in organic solvent is poured in to an agitated aqueous solution. The organic solvent rapidly partitions in to the external aqueous phase and the polymer precipitates around the organic solvent. The subsequent evaporation of the entrapped organic solvent leads to the formation of internal cavities within the microspheres. ⁹

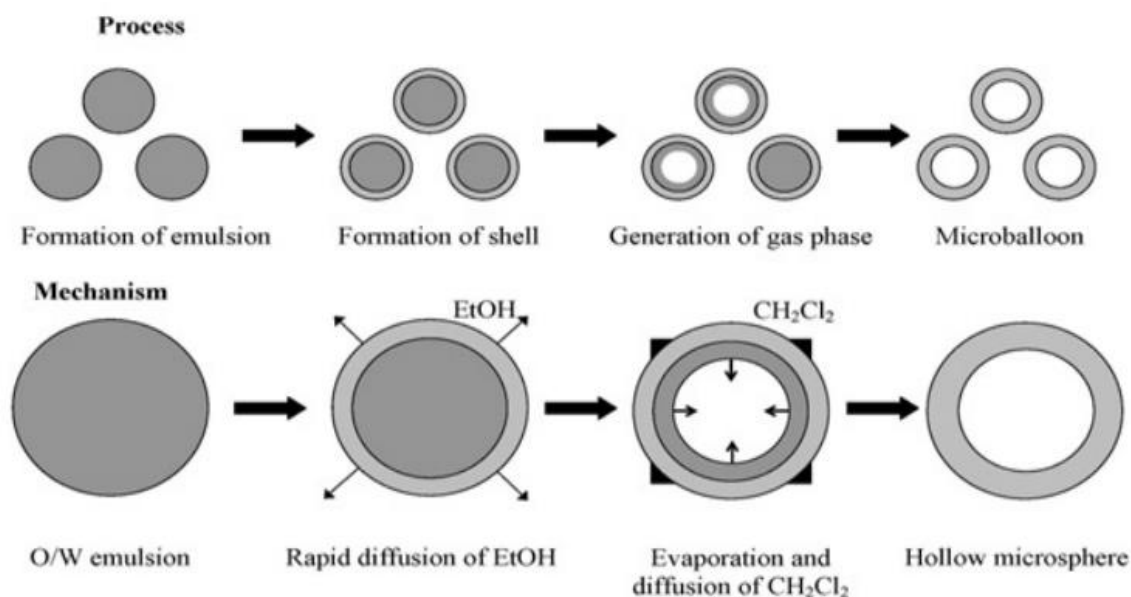
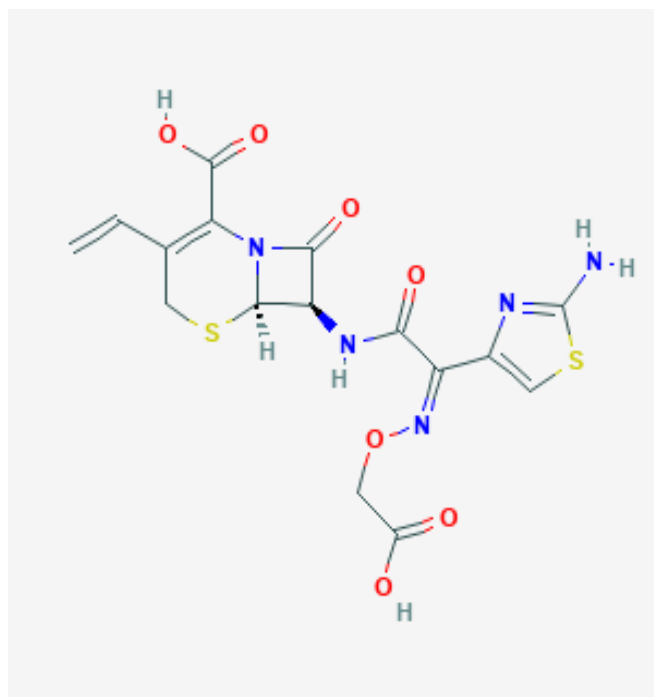


Figure 3: Mechanism of hollow microspheres

Drug Profile:

Structure of Cefixime



- **Drug:** CEFIXIME
- **Chemical Formula:** $C_{16}H_{15}N_5O_7S_2$
- **Molecular weight:** 453.5 g/mol
- **Chemical name:** (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid.
- **Category:** Anti-biotic

- **Solubility:** Soluble in methanol; sparingly soluble in ethanol (95 per cent); practically insoluble in ethyl acetate and in water.
- **MOA:** The bactericidal action of Cefixime is due to the inhibition of cell wall synthesis, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death.
- Cefixime is an orally active 3rd generation cephalosporin antibiotic.
- Cefixime is a weak acid which is primarily absorbed from the stomach and upper part of intestine.
- It has an oral bioavailability of about 40% - 50% and plasma half-life 3-4 hrs.
- According to the Biopharmaceutical Classification System (BCS), cefixime belongs to BCS class IV drugs, which are often characterized by low permeability and low solubility, resulting in its limited and variable oral bioavailability.

II. Method of Formulation of Hollow Microspheres:

Emulsion Solvent Diffusion Technique

1. Polymer + Organic solvents
2. Drug + Organic solvent
3. Polymer solvent + Drug solvent mixed using magnetic stirrer.
4. Added drop wise using syringe the Drug and Polymer solution was dropped into PVA 1% Solution.
5. After emulsification organic solvent is evaporated by continuous stirring by 3 blade mechanical stirrer at 300 rpm for about 20-40 min.

Ingredients	Quantity in mg
Drug (Cefixime)	500
HPMC 50cps	500
Polyvinyl Alcohol	1%
Ethanol (ml)	10
Dichloromethane	5
Drug: Polymer	1:1



III. EVALUATION PARAMETERS OF HOLLOW MICROSPHERES

1. Determination of Solubility

Solubility of Cefixime was performed in solvents and was soluble in Distilled water, ethanol, di-methyl formamide, methanol, 0.1N HCl, 7.4 Phosphate Buffer, 6.8 Phosphate Buffer.

2. Melting point determination

Melting point of Cefixime was determined by using Thiele's tube method. Liquid paraffin was filled in Thiele's tube and the sample was loaded in capillary tube, tied to thermometer and immersed in the Thiele's tube. Melting point of a drug sample has been the first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by the lowering as well as raise in the melting point.

The melting point of Cefixime was determined by using Thiele's tube method and was found to be in the range of 207°C - 218°C, which complied with Indian and European Pharmacopeia Standards, thus indicating purity of obtained Cefixime sample.

3. Spectroscopic Studies

Stock Solution A

100mg of Cefixime is accurately weighed and transferred to 100ml of volumetric flask, 50ml of methanol is added and sonicated. The volume was made up to the mark with methanol to give 1000µg/ml solution.

Stock Solution B

To prepare working stock solution, 10ml of stock A was pipetted and transferred into 100ml volumetric flask and made up to the volume of 100ml using distilled water.

Working Standard solution

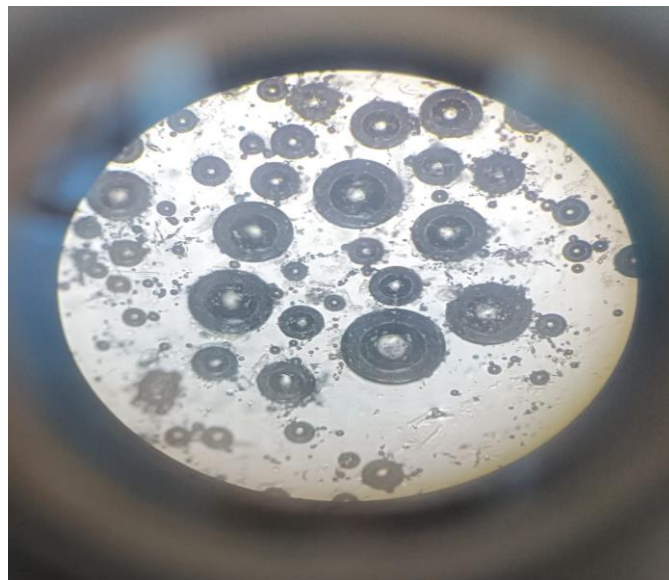
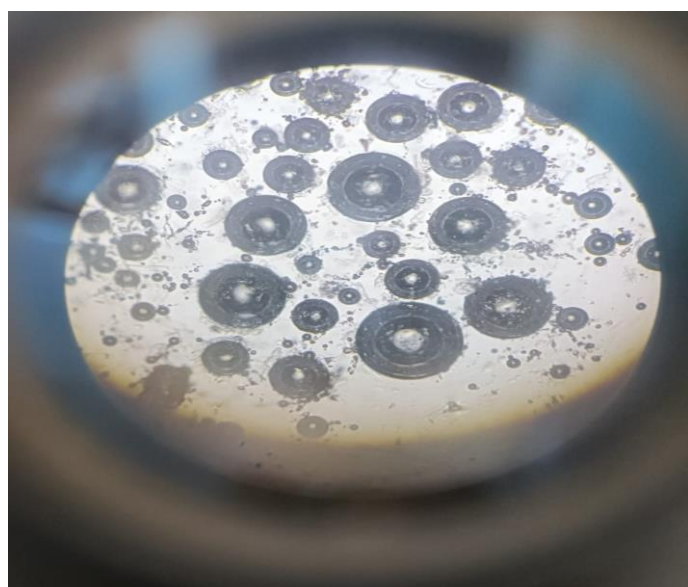
To prepare calibration standards, pipette out 2, 4, 6, 8, 10ml of stock solution B into 10ml volumetric flasks and were diluted up to the mark using distilled water to obtain drug concentrations of 2, 4, 6, 8, 10µg/ml and linearity was studied against a reagent blank as reference at 287 nm.

Calibration curve of Cefixime

- The absorption maxima of Cefixime were found to be 254nm by using methanol as a co-solvent.
- The regression co-efficient of Cefixime was found to be 0.9989 and the slope value was found to be 0.0541, which showed a linearity between absorbance and concentration

4. Particle Size

The particle size of the formulated microsphere was found to be **560-570 nm**.



5. Percentage Yield:

The percentage yield of Cefixime was found to be **85.10%**.

6. Drug Entrapment Efficiency

Highest entrapment efficiency of cefixime hollow microspheres was found to be 89.34%. As the polymer concentration was increases the entrapment efficiency also increases.

7. Percentage yield

A 100% yield could not be achieved principally due to adhesion of hollow microspheres on to the stirring blade. The Percentage yield were found to be in the range of 81.21% to 91.03%.

IV. CONCLUSION

There is a need to develop a new dosage form for Cefixime for reducing its side effects, maintaining therapeutic index over a period of time, sustaining the drug for long time, also for targeting the drug to the specific site for good patient compliance. The objective of the study was to prepare hollow microspheres loaded with anti-infective drug, using emulsion solvent diffusion method. The formulation behaviour was studied by varying the drug and polymer ratio and keeping the drug concentration constant. The prepared hollow microsphere formulations were characterized for particle size, surface morphology, drug entrapment efficiency, in vitro drug release, release kinetics. The method of preparation of hollow microspheres was found to be simple and reproducible. The prepared hollow microsphere containing ethyl cellulose and eudragit L-100, as a carrier exhibited good solubility, cumulative drug release from formulation. At the initial 1 hour the release of the drug was slow and gradually increased by the end of 12 hours.

Hollow microsphere formulation is simple, economical with increased patient compliance. Using innovative ideas and new scientific challenges, the field of hollow microspheres shall continue to develop interest within the chemical research community. Further investigation is fostered to design a high yielding, affordable, reproducible process that can be implemented for large scale production in short period time. Hence, extensive research is essential to study unwanted effects on health.

REFERENCES:

1. Prajapati VD, Jani GK, Kapadia JR. Current knowledge on biodegradable microspheres in drug delivery. Expert opinion on drug delivery. 2015 Aug 3; 12(8): 1283-99.
2. Yadav VK, Gupta AB, Kumar R et al., Mucoadhesive polymers: means of improving the mucoadhesive properties of drug delivery system. J. Chem. Pharm. Res. 2010; 2(5): 418-32.
3. Gautam A, Ahmed T, Batra V et al., Pharmacokinetics and pharmacodynamics of endoperoxide antimalarials. Current drug metabolism. 2009 Mar 1; 10(3): 289-306.
4. Shen SI, Jasti BR, Li X. Design of controlled-release drug delivery systems. Standard Handbook of biomedical Engineering & Design. New York: McGraw-Hill. 2003: 161-79.
5. Martinez-Ballesta M, Gil-Izquierdo A, Garcia-Viguera C et al., Nanoparticles and controlled delivery for bioactive compounds: Outlining challenges for new "smart-foods" for health. Foods. 2018 May; 7(5): 72.
6. Jain KK. Drug delivery systems-an overview. Drug delivery systems. 2008: 1-50.
7. Uhrich KE, Cannizzaro SM, Langer RSShakesheff KM et al., Polymeric systems for controlled drug release. Chemical Reviews-Columbus. 1999 Nov 10; 99(11): 3181-98.
8. Fusco S, Cariati D, Schepisi R et al., Management of oral drug therapy in elderly patients with dysphagia. Journal of Gerontology and Geriatrics. 2016 Mar 15; 64: 9-20.
9. Torres-Martinez EJ, Cornejo Bravo JM, Serrano Medina A et al., A summary of electrospun nanofibers as drug delivery system: Drugs loaded and biopolymers used as matrices. Current drug delivery. 2018 Dec 1; 15(10): 1360-74.
10. Germain M, Caputo F, Metcalfe S et al., Delivering the power of nanomedicine to patients today. Journal of Controlled Release. 2020 Oct 10; 326: 164-71.
11. Hamman JH, Enslin GM, Kotzé AF. Oral delivery of peptide drugs. BioDrugs. 2005 May; 19(3): 165-77.