Review Article

Post-Expansible Hydrogel Foam Aerosol of PG-Liposomes: A Novel Delivery System for Vaginal Drug Applications

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Received 25 April 2013; accepted 17 May 2013

Abstract

The post expansible hydrogel foam aerosols of propylene glycol-embodying liposomes (PG-liposomes) (PEHFL) are recent novel drug delivery for vaginal applications. The conventional dosage forms are not easily penetrated through vaginal mucous membrane due to particle size, limited contact time with vaginal mucosa. Conventional gel not spread uniformly in vaginal canal because their higher viscoelasticity. So overcome this problem the PEHFL are used for vaginal treatment. The propylene glycol-embodying liposomes (PG-liposomes) which composed of phospholipid, propylene glycol (PG) and water, was introduced as a carrier of drugs. PG-liposomes showed high entrainment efficiency, more stable and smaller particle size which are easily penetrated the highly folded epithelial vaginal membrane. Aerosol foams have some distinct advantages for VDDS including greater degree of spread, ease of application; enhance topical drug delivery efficiency and comfortable feeling. In addition, the potential of contaminating the unused portion of the medication is minimized as the foam is often administered from a sealed airtight container. As a result of their benefits, patient compliance is greatly improved with foams and direct apply on the infection site so the minimum quantity of drug needed and max amount of drug reached the site of infection. The main advantages of PEHFL over conventional dosage forms are the ability to enhance the vaginal mucosa permeability of drug, spread uniformly in vaginal canal especially the highly folded epithelial surfaces, prolong the residence time at the site of administration and induce drug delayed release. In conclusion, the PEHFL may be a promising delivery system for vaginal delivery of medication.

Key words: Hydrogel foam, Post- expansible, PG-liposomes, vaginal drug delivery, Swelling, Spreading, Diffusion

1. INTRODUCTION:

Vaginal inflammation is a commonly encountered and frequently occurring gynecological disease, mainly including vaginitis and cervical erosion. Clinical treatment of vaginal inflammation, medication usually is administered by oral, intramuscular injection or vaginal route. Vaginal route namely vaginal drug delivery system (VDDS) is more comfortable and convenient to administer for local targeted treatment. VDDS has many advantages, such as avoiding gastrointestinal tract adverse reaction and first-pass liver metabolism after oral ingestion, and also prevents the uncomfortable and sometimes painful intramuscular injection. Moreover, VDDS could preferentially deliver high levels of medication directly to the uterine circulation (“first uterine-pass effect”), thereby providing high levels of drug to the endometrial tissue and caused much greater topical effects. Liposomes is a spherical vesicle with a membrane composed of a phospholipid bilayer used to deliver drug or genetic material into a cell (Fig 1). Liposomes can be composed of naturally derived phospholipids with mixed lipid chain like egg phosphatidylethanolamine. Various drugs from low molecular weight (glucose, synthetic drugs, etc.) to high molecular weight (peptides and proteins, DNA, etc.) have been incorporated in liposomes. The water soluble/hydrophilic drugs are present in aqueous compartments while lipid soluble and amphiphilic drugs trap themselves in phospholipid bilayer. Hydrogel is a network of polymer chain that are water insoluble, in which water is the dispersion medium. Hydrogel are containing 99% of water. Hydrogel also possess a degree of flexibility, due to their significant water content. 2. ADVANTAGE OVER CONVENTIONAL DOSAGE FORMS

The efficacy of all Conventional dosage forms is greatly decreased by the fact that the drug cannot spread in vagina fully and contact the disease sites which located in vaginal mucous membrane folds namely rugae tightly, and the
induced irritation by higher local drug concentration or by insoluble ingredients is another obvious deficiency. In addition, conventional dosage forms are susceptible to removal by the self-cleansing action of the vaginal tract, this limiting contact time of administered drugs with vaginal mucosa and impairing therapeutic efficacy of the drug makes multiple and frequent administrations necessary for vaginal targeted therapy. The patients’ comfortable feeling in administering these dosage forms is also a critical component. It is reported that patients are generally to tolerate gels better than other dosage forms. However, there is an obviously shortcoming, it is very difficult for classic gel to spread uniformly in vaginal canal because their higher viscoelasticity. Aerosol foams have some distinct advantages for VDDS including greater degree of spread, ease of application, enhance topical drug delivery efficiency and comfortable feeling.

**Fig 1. Spherical Formation of Liposomes**

**3-AIM**
1- To achieve better vaginal mucosa permeability.
2- A long retention time to maximize drug release.
3- A proper spreading over the vaginal epithelium to obtain fast absorption or to maximize the effect in case of local treatment and,
4- Be easy to administer (allow self-administration) and not cause discomfort to improve patient compliance.

**4-FORMULATION OF PEHFL**

**4.1 Materials used and its importance**
Hydroxyethyl Cellulose(HEC), Difluoroethane propellants (HFC), sodium dodecylsulfate (SDS) , propylene glycol (PG) , Soya phosphatidylcholine (SPC) and cholesterol (CH).

Hydroxyethyl Cellulose(HEC) is a gelling agent which are used for the formulation of gel, HFC are propellant which act as a vehicle for discharging the content of an aerosol container, SPC is major constituent of cell membrane, it also dispersing, emulsifying, and stabilizing agents, CH also used as a stabilizer.

**4.2 Preparation of PG-liposomes**
PG-liposomes are prepared by modified thin-film homogenization method (Fig 2). The dehydrated alcohol solutions of SPC and CH are pipetted into a flask. After vortexing to ensure thorough mixing, the solvent is completely dried in a rotary evaporator to form a thin lipid film on the wall of the flask. The drug are dissolved in 1/3 volume of the aqueous phase of PG in water which preheated at 50°C, then add into the flask and the dried thin lipid film are hydrated by rotation at the corresponding temperature. The preparations are homogenized by using homogenization for 10 min.

**Fig 2. Rotary flash evaporator**

**4.3 PREPARATION OF DRUG LOADED PEHFL**
SDS and HEC are dissolved in PG-liposomes suspension. After mixed thoroughly, the resulting preparation are added to a container and sealed with a gate. Finally, HFC are added to the container by using pressurized filler. Similar procedures are carried out to prepare PLFA with the formulation .hydrogel (HYG) are prepared by dissolving drug , PG and SDS in deionized water to which HEC are added, then the resulting preparation was mixed uniformly. The HYG are added to a container, then HFC are added as above mentioned, as a result, the HFA are obtained.

**5-CHARACTERIZATION OF DRUG LOADED PEHFL**

**5.1 Foam swelling behavior and duration**
The foam swelling of gel in room temperature (20°C) and body temperature (37°C) after spurted from a sealed container by using a digital camera, and the foam duration are defined as the time when the volume of foam dollop decreased to 85% of its maximum volume.

**5.2 Evaluation of mucoadhesive force**
The two pieces of porcine vaginal tissue membrane (2.0 cm × 2.0 cm) are fixed on two same planks, respectively. One plank is fixed on a stainless steel base; the other are connected with a firm thread which fastened a light plastic beaker through a fixed little crown block (Fig.3). The preparation 1.0g is placed at between two pieces of porcine vaginal tissue, and then slightly press upper plank using hand for 10 s. Next, water is dropped into the beaker at a speed of 1.0 ml/min until the two planks are pulled apart by the gravity of water. The beaker containing water is weighed and the mucoadhesive force are calculated accordingly.

**Fig 3. The device used in the measurement of mucoadhesive force.**
5.3 In vitro drug release
Frozen porcine vaginal tissue specimens are thawed in physiological saline for 25 min, and one end of the thawed vaginal tissue specimens were carefully sealed with a thread. Then drug loaded various formulations are packed into a porcine vaginal tissue, by carefully inserting a plastic conduit attached to a sealed container (for PEHFL, PLFA and HFA) or a syringe (for HYG). After intravaginal administration of drug loaded formulation, the specimen are placed in an Erlenmeyer flask, and the unsealed end are fixed at beak by a stainless steel keeper pincers. The release medium is physiological saline, and the medium was maintained at 37°C and shaken. At 2-h intervals, 0.1 ml of dissolution fluid was collected and replaced with equal volume of fresh medium. The withdrawn supernatant was analyzed for drug content using HPLC assay method.

6-CONCLUSION
Vaginal drug delivery is a promising route for local and systemic drug delivery, by this delivery route the first-pass liver metabolism after oral ingestion and the uncomfortable and painful intramuscular injection can be avoided. In addition, due to the presence of a dense network of blood vessels and lymphatic vessels surrounding the vagina, rapid absorption can be obtained. The advantages of PEHFL are the ability of laggingly swelling after delivered in the vagina and the better adhesion properties, this PG-liposomes which contribute to the superior delivery properties distribute uniformly throughout the vaginal cavity and contact the vaginal mucous membrane tightly for a long time. Effectiveness of drug would be greatly enhanced and the irritation or side effects induced by local higher drug concentration would be avoided. These reviews indicate that the post-expansile foam aerosol of PG-liposomes (PEHFL) may be a promising delivery system for vaginal drug delivery applications. Drug would be greatly enhanced and the irritation or side effects induced by local higher drug concentration would be avoided.

REFERENCES

Source of support: Nil; Conflict of interest: None declared