**Academic Journal of Science and Technology**
ISSN: 2771-3032 | Vol. 1, No. 3, 2022

# Development and Application of Suppositories in Modern Pharmaceutics

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**Abstract:** Suppositories have a long history of development and have become one of the commonly used dosage forms for clinical use. With the continuous development of formulation technology, researchers have developed a variety of novel formulations, making them not only limited to topical medication, but also can be absorbed by the luminal tract to the blood to play a systemic role. This article mainly provides a brief review of the introduction, matrix species, characteristics, and novel suppositories.

**Keywords:** Suppositories, Pharmaceutical agents, Research advances.

## 1. Embolic Background Introduction

Suppositories, one of the common dosage forms of drugs, have a long history in China, and ear plugs, nasal plugs, anal plugs, vaginal plugs, urethral plugs, etc. are contained in the compendium of Materia Medica by Li Shizhen in the Ming Dynasty [1]. At first, it was only applied for topical use such as lubrication, sterilization, local anaesthesia, anti insect and convergence, and later with the development of technology, people have found that drugs in suppositories can exert systemic therapeutic effects through intestinal mucosal absorption in addition to the above functions. With the development of pharmaceutics, so that suppositories have also been further developed.

The commonly used matrices for suppositories are divided into an oily matrix and a water-soluble matrix. The oily matrix cocoa bean fat is a solid fat that is stable, rapidly melts, and is non irritating, but is used less often because of its high price. The water-soluble matrix is mainly glycerol gelatin and polyethylene glycol (PEG). Glycerin gelatin systems are made of gelatin, glycerin and water, are elastic, do not break easily, can slowly dissolve in the secretory fluid after sealing into the lumen, and can prolong the drug's efficacy, but the dissolution rate changes as the ratio between gelatin, glycerin and water changes, so the preparation of such suppositories requires different matrix ratios depending on the therapeutic purpose.

Some additional agents are also added to suppositories, and features may include absorption enhancers, absorption blockers, plasticizers, and others. In the hope of improving matrix stickiness and increasing drug efficacy.

Preparations of suppositories can be divided into 3 types: kneading, cold pressing, and hot dissolving. General oily matrices employ any of 3 methods, while water-soluble matrices mostly employ hot-melt method [2].

A qualified suppository should have the following requirements (1) the drug and matrix should be mixed and uniform, and the external shape of the suppository should be complete and smooth, without irritation. (2) After clogging into the lumen, it should melt, soften or dissolve, and mix with the secretory fluid to gradually release the drug, producing local or systemic effects. (3) Suitable hardness to avoid deformation during packaging, storage or use [3].

For systemic administration, compared with oral preparations, suppositories have a relatively rapid absorption and onset of action, a small first pass effect on the liver, and better efficacy, but also avoid irritation to the gastrointestinal tract, and are more convenient for rectal administration to patients or children who do not adhere well to medication, therefore, suppositories have obvious advantages in antipyretic and pain relieving medication. Also suitable for non oral drugs and other advantages, so that suppositories play a unique therapeutic effect in the treatment of luminal diseases, gynecological diseases, rectal diseases. In addition, compared with oral or injectable administration, the distribution of drugs after the administration of suppositories is more concentrated, the concentration of drugs at the lesion site is high, the efficacy is improved, the drug is less distributed in other sites, and its adverse effects are greatly reduced.

## 2. Types of Suppositories

### 2.1. Homogeneous Plain Suppositories

Homogeneous common suppositories the main ones common according to their route of administration are the anal and vaginal ones. Conotruncal, torpedo shaped) are common. Among them, those with torpedo shape are more able to adapt to the contraction of the anal sphincter and are easily introduced to the rectum. Suppositories used in adults are generally about 2 g, with a length of 3 to 4 cm, and in children about 1 g, reduced as appropriate for age; The shape of the vaginal plug was mainly spherical, ovoid, duckbill and fusiform, and each plug weighed 2-5 g and measured 1.5-2.5 cm in diameter. Other suppository types are urethral plugs, nasal plugs, ear plugs, etc. [4].

### 2.2. Double Layered Plugs

Common single-layer suppositories will move deep to the administration site upon fusion, and deep drugs enter the liver via the rectum after being absorbed intravenously, thus having a first pass effect, affecting the bioavailability of drugs. In order to allow the effective absorption of suppository drugs in the lower rectal vein, a double layered suppository composed of a water-soluble matrix plug (intrarectal absorption of secretory fluid to form a gel to inhibit the diffusion of drugs from the lower rectum to the upper part) together with a drug containing plug was designed.

The characteristics can be classified as follows: dispersing two or more drugs with different physicochemical properties into a lipid soluble mechanism or a water-soluble mechanism, respectively, to make suppositories containing upper and lower two layers, facilitating drug absorption or avoiding compatibility contraindications that may occur with drugs; The upper and lower layers were made with blank matrix and drug containing matrix, and the upper layer of blank matrix was utilized to block the upward diffusion of drugs, so as to reduce the drug absorption from the superior rectal vena cava, in order to improve the drug availability and reduce the adverse effects of drugs; A drug is prepared as upper and lower two layers by dispersing in a lipid soluble matrix and a water-soluble matrix, respectively, which enables suppositories to have both immediate and sustained release effects when used; Suppositories from the inner and outer bilayers, since the outer layer first dissolves and then the inner layer dissolves and fuses, can exert the effects of both drugs. Qiu Gui Zhou et al [5] prepared the lower pharmaceutical layer of aspirin bilayer suppositories by mixing fatty acid glycerolipids with lipid soluble matrix, and the upper blank layer of aspirin bilayer suppositories was prepared with water-soluble matrix. Effectively prevent the upward diffusion of drugs released from traditional aspirin anal suppositories, avoid the absorption of some drugs through the portal hepatic system, and improve the bioavailability of aspirin. Household Juan zhang [6] prepared as double layered suppositories by using bitter bean extracts for local vaginal delivery, and used the slow-release characteristics of double layered suppositories to prolong the retention time of drugs and exert long-lasting and stable drug effects, in the hope of providing a safe and long-acting new double layered suppository for the treatment of gynecological inflammation.

## 2.3. Hollow Plugs

With the development of suppositories, Tandou Shanfeng et al developed hollow suppositories (HTS) in 1984, whose outer layer is a shell made of matrix and hollow can be filled with drugs in various states such as solid, liquid and suspended States, HTS offers the possibility of rectal drug delivery for many drugs due to its rapid drug release, high bioavailability and wide application range compared with common suppositories. Hollow plugs for rectal drug delivery improve systemic effectiveness. Previous data of bioavailability indicated that hollow type suppositories were more effective for the absorption of part of the drug compared with conventional suppositories. Haiyu pan [7] and others prepare nimesulide into a hollow suppository so that it can quickly reach the effective blood drug concentration and maintain the concentration for a long time, indicating that this hollow suppository not only enables the rapid onset of drugs and maintains the treatment for a longer time, but also has a slower peak blood concentration and reduces drug toxic side effects. Peng Hao Chen et al [8] used commercially available pediatric ibuprofen plugs as a control to investigate the in vitro dissolution of the self-made hollow plugs. The results showed that both hollow plugs reached dissolution equilibrium within 20 min with dissolution rates greater than 90%; However, the dissolution rate was 79% at 70 min, which suggested that the hollow plug could achieve rapid drug release.

## 2.4. Microcystic Plugs

Compared with common plugs, microcapsule plugs have the advantages of sustained release and low toxicity, as well as stable blood concentration and long maintenance time. Yihua Yang et al [9] prepared naproxen microcapsule plugs and compared the cumulative drug release rate in vitro with naproxen plain plugs. It confirmed that the preparation process of naproxen microcapsules was simple and quality controlled, and it had a better sustained effect. Lei Wang [10] et al used a reaggregation method to prepare acetaminophen (AAP) microcapsules and investigated its in vitro drug release behavior. The prepared composite microcapsule plugs have better drug release characteristics compared with common suppositories.

## 2.5. Effervescent Plugs

In comparison with common suppositories, Effervescent Suppositories are particularly suitable for gynaecological diseases because they can produce large quantities of foam after disintegration, thus increasing the contact area between the drug and the lesion site and better exerting their efficacy. Jun Yong Jiang [11] et al., used semi synthetic fatty acid glycerides as suppository matrix, sodium bicarbonate, citric acid as foaming agent, danazol as main drug, to prepare effervetory plugs, and the produced foam prolonged the drug action time with mucosa as well as contact area, increased the drug concentration in local tissue, and then enhanced the drug therapeutic effect. Kai Li Zhang and others [12] used povidone iodine, sodium bicarbonate, citrate and duckbill shaped suppository molding to prepare povidone iodophore plug, and it was found that the preparation process of povidone iodophore plug was simple, stable and convenient for quality control, which did not affect the iodine content when stored at low temperature and had a long validity period of 432d.

## 2.6. Sponge Plugs

Compared with common suppositories, sponge suppositories can be persistently dispersed on the mucosal surface of the luminal tract, avoid the deficiency of loss due to matrix melting, and maintain their efficacy for a long time, which is generally vaginal. The common matrix is gelatin, and the produced suppositories can be enzymatically absorbed in vivo for convenient use. A sponge vaginal plug of tinidazole developed by Meng Shengmen et al. [13] and in vitro tests proved that it had a slow-release effect; Clinical observations have shown that this formulation has high efficacy, short treatment duration and little side effects, and it is of value for widespread use. Xu Ziyou et al [14] demonstrated that compared with metronidazole suppositories based on polyethylene glycol, metronidazole vaginal sponge suppositories based on polyether type polyurethane foam were long-lasting, safe, and convenient to use.

## 2.7. No Thrombolytic Agent Thrombolysis

Insoluble suppositories, which are neither dissolved nor disintegrated in the rectum, exert their efficacy by absorbing moisture that gradually swells, slowly releasing the drug. A long-acting lidocaine plug developed by the inveresk Institute in the United Kingdom, using hydroxypropyl methylcellulose of relative molecular mass 200000 as matrix and 25% drug release in 1 h and 65% drug release in 4 h, could maintain effective blood concentration for up to 24 h [15].

## 2.8. Gel Suppository Plugs

Compared with common suppositories, the foreign body

sensation generated after the incorporation of suppositories into the body cavity can be avoided due to the fact that the gels have a special adhesive force to the biological mucosa, which can prolong the retention and release time of drugs to promote the absorption of drugs and improve the bioavailability of drugs. Huoshinmei [16] used white clear gelatinous semi-solid water-soluble gel composite tinidazole hydrogel plugs fabricated from tinidazole, chlorhexidine acetate, clotrimazole with matrix poloxamer P407, Carbomer and other excipients processed by advanced processes to improve the traditional suppositories' inability of sustained and constant drug release and susceptibility to body temperature, which resulted in liquid like efflux of matrix after thawing and contaminated clothing. The Compound Tinidazole hydrogel plug has a high local concentration in the vagina after use, no adverse effects have been reported at this time, and it can be released continuously in a stable manner to achieve sustained release.

## 2.9. Sustained Release Thrombus

Sustained release suppositories, suppositories made by encapsulating drugs into a plastic insoluble polymeric material, do not dissolve at the site of administration, the drug must first diffuse out of the insoluble matrix and slowly release the drug through the dissolving effect of mucosal fluid, so as to play a retarding role in the dissolution and release of the drug [17]. In the development of indomethacin sustained-release suppository and determination of its bioavailability, it was found that this formulation exhibited reduced peak concentration, prolonged time to peak, and distinct sustained-release profile compared with common suppositories [18]. He Xin et al. [19] used metronidazole and miconazole nitrate as the main drugs, hydroxypropyl methylcellulose as the backbone material, and used hot-melt method to prepare sustained-release suppositories, which compared with common suppositories can not only prolong the drug efficacy and reduce the administration frequency, but also flatten the release of drugs, and can maintain effective drug concentrations to maintain treatment.

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