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Liquid Suppositories: A Review on Novel Approach of Rectal Drug Delivery System

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ABSTRACT

Drug delivery through the rectum is a helpful substitute for oral administration forthose who cannot swallow.Despite its obvious benefits, rectal medication administration is not used enough. Rectal delivery of drugs promotes rapid absorption and high bioavailability, with a subsequent immediate onset of pharmacological effect. Historically, localized treatments such as the administration of laxatives and the treatment of hemorrhoids have been accomplished through the use of traditional rectal dose forms. However, the recent trend is showing an increase in the development of novel rectal delivery systems, one of which is liquid suppositories. Conventional suppositories are solid forms that often cause discomfort during insertion. Patients also feel unpleasant when suppositories leak out of their rectum. Further, the medications may experience the first-pass impact when the mucoadhesivity-free solid suppositories make it all the way to the colon's end.Mucoadhesive, thermosensitive, in situ-gelling liquid suppositories with a gelation temperature of 30 to 36°C are designed to address these issues, suitable gel strength, and bioadhesive force.This article focuses on an overview of liquid suppositories including introduction, advantages, thermosensitive liquid suppositories, application, method of preparation andevaluation parameters,etc. Thus, it may be said that liquid suppositories represent a promising alternative to conventional solid suppositories.

Keywords: Liquid suppositories, mucoadhesive, gelation temperature, bioadhesive force.

INTRODUCTION

The easiest and most convenient way to administer medication is orally, which is why it is the suggested method for regular use. This is not practicable, though, in certain situations (e.g., before surgery, during nausea/vomiting or convulsions, in patients who are not cooperative). Rectal administration is now a well-known method of drug delivery, and it might be a good alternative in some circumstances [1].

Traditionally, localized treatments such as the administration of laxatives, hemorrhoid treatments, and antipyretics have been administered via rectal dose forms. On the other hand, a recent trend indicates a rise in the creation of innovative rectal delivery methods that use porto systemic shunting to transfer the medication straight into systemic circulation.

Furthermore, with the help of cutting-edge Rectal Drug Delivery Systems (RDDSs) and contemporary pharmaceutical items, greater bioavailability and regulated drug release are now achievable. These systems can be altered to function locally or globally, and they can release the active substance either instantly or gradually.

There are four types of traditional rectal dose forms: semi-solid (gel, ointment), liquid (microenema, enema, suspension, foam, and suspension), solid (suppository), and medical devices (rectal tampon). When it comes to rectal medicine administration, solid suppositories have historically been the most often utilized delivery method. They account for more than 98% of all rectal dose types. Drug-containing suppositories that are suspended or dissolved in a suppository substrate and release the active ingredient for either local or systemic activity when they melt or dissolve at physiological circumstances [2].

Furthermore, most medications' rectal absorption is frequently irregular and unexpected. Due to the rectum's low fluid content and the anus's modest absorption surface area, dissolving issues may arise. Conventional suppositories also have the disadvantage of having a melting point that is close to room temperature in tropical areas. It was possible to see some of the storage and transportation issues. Recent improvements to traditional RDDSs have been made by adjusting the formulation's characteristics, such as the gelation strength and temperature.

Better pharmacokinetic profiles, local therapeutic effects, and enhanced bioavailability can be achieved through extended retention and controlled release of the drug.

RDDS was developed to provide greater control over the drug's distribution, retention, and/or release through a range of formulation approaches. New rectal drug delivery technologies have made it possible to distribute drug molecules more precisely for local or systemic

effects. These technologies include hollow-type suppositories, thermo-responsive and muco-adhesive liquid suppositories, and nanoparticulate systems integrated into the right vehicle [3].

Compared to the oral route, the rectal route offers the following benefits for medication delivery:

a) The quick absorption of various low-molecular-weight medications.
b) Possibility of lymphatic system absorption and partial inhibition of first-pass metabolism.
c) The retention of larger doses of the medication.
d) The likelihood of effective drug absorption and delivery.
e) Very little first-pass drug metabolism because the suppository is inserted into the rectum at a reasonable distance.
f) Preventing irritating medications, such as non-steroidal anti-inflammatory drugs, from coming into contact with the stomach mucosa.
g) Increased effectiveness [4].

Medicated solid dose forms that melt or soften at body temperature are called traditional suppositories. This is the perfect dosage form for children, neonates, and unconscious patients. The fact that the medications administered via suppositories avoid the first-pass effect sets them apart from other oral dosing forms. Regrettably, traditional solid suppositories have been plagued by side effects like pain, discomfort, and an unfamiliar sensation. Many medications absorb unevenly or poorly through the rectal mucosa; a solid-type suppository, which may reach the end of the colon, may also allow pharmaceuticals to undergo the first-pass effect. Additionally, medications can be metabolized in rectal mucosa and bacteria. Furthermore, some suppositories either "leak" or are ejected after being inserted.From an industrial perspective, solid suppositories are difficult to make and manage since they must be melted and then filled into a vessel by a heating process. To keep the suppositories in their original shape until they are administered, the vessel must be packaged together.

In order to address the issues with traditional solid suppositories, it would be ideal to create a liquid suppository that gels at body temperature, has a strong enough gel to prevent leakage from the anus after administration, and has a weak enough bioadhesive force to stay inside the colon. As a result, liquid suppositories were created to overcome the drawbacks of solid suppositories, including discomfort and anus leaks. Simple to use, liquid suppositories do not harm mucosal layers, act as a mucoadhesive to the rectal tissue without leaking, and lessen

the sensation of a foreign substance in the anus. Based on research projects completed through the year 2023, the current review [5].

Thermosensitive liquid suppositories:

Many medications, including those with anticancer, analgesic, antiemetic, antihypertensive, psychiatric, antiallergic, anesthetic, and antimalarial properties, can be administered with thermosensitive liquid suppositories. Furthermore, thermosensitive devices offer more control over the release of medication by varying the kind and quantity of components. This approach could potentially increase the effectiveness of drugs. The kind of components (mucoadhesive and thermosensitive polymers) and their concentration determine this dosage form's characteristics [6].

The primary benefits of thermosensitive liquid suppositories over traditional or solid suppositories are as follows:

a) The fact that they stay liquid at lower temperatures makes them simple to provide to the anus.
b) After administration, function as a mucoadhesive to the tissues of the rectal area, preventing leaks.
c) Do not cause any harm to mucosal layers [7].

The thermosensitive liquid suppository must have appropriate mechanical and rheological characteristics in order to be utilized for therapy, such as:

a) Gelation temperature: The degree of heat at which the liquid and gel phases separate. For rectal administration, the gelation temperature range that would be suitable is 30-36.5 °C.
b) Viscosity: The term "gel strength" refers to the viscosity of a thermosensitive liquid suppository at 36.5 °C. A liquid suppository with an ideal gel strength of 10–50 s will stay in the upper portion of the rectum and not leak out of the anus.
c) Gelation time and gel strength: A thermosensitive liquid suppository that has an ideal gel strength and a comparatively quicker gelation time will stay in the upper portion of the rectum and not leak out of the anus. The term "gelation time" refers to how long it takes a thermosensitive liquid suppository to reach a viscosity of about 4000 mPa·s at 36.5 °C. Gelation time varies according to suppository composition but is usually 2–8 min.
d) Mucoadhesive force: The strength with which the thermosensitive liquid suppository adheres to the rectal mucosal membranes[8].

The properties of the polymers used to create thermosensitive liquid suppositories are as follows:

Thermosensitive rectal gels are known as liquid suppositories. Because the formulation's foundation material is a thermosensitive polymer, which gels at 37 °C, a physiological temperature, they are also known as thermosensitive liquid suppositories. Liquid preparations can be made because the transition sol-gel temperature (Tsol-gel) is lower than body temperature and allows the preparation to get back at body temperature [9]. When used in the right concentration, thermosensitive polymers like pluronic or poloxamers form a gel at physiological temperature, limiting excessive spreading and leaking in the rectum. Furthermore, compared to the thermosensitive polymer alone, the combination of mucoadhesive and thermosensitive polymers enables longer prolonged drug release [10]. Drugs are more likely to be absorbed systemically when the hydrogel is immobilized for an extended length of time in the rectal cavity due to the development of mucoadhesive characteristics. The manufacture of a thermosensitive liquid suppository involves several key components, including viscosity, gelling time, and temperature threshold [11].The most popular base of thermosensitive liquid suppositories are poloxamers (triblock copolymers of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) (PEO–PPO–PEO)). They comprise a central block of hydrophobic polypropylene oxide (PPO) surrounded on both sides by blocks of hydrophilic polyethylene oxide (PEO) [12]. In the pharmaceutical industry, thermosensitive systems that are most frequently encountered are triblock copolymers (Pluronic® or Poloxamer® class). Recently, thermosensitive and mucoadhesive polymers have drawn a lot of interest for their ability to provide an enduring form of delivery while also reducing patient discomfort and alienation caused by solid suppository insertion[13].

In general, the concentration of poloxamers determines their phase transition temperature. Aqueous solutions of poloxamer remain fluid below Tsol-gel, and beyond this temperature, the solution changes into a semi-solid substance. Poloxamer copolymer chains interact hydrophobically to produce thermogelation. The chain of poloxamer copolymer start to clump together form a micellar structure as the temperature is elevated. In cold water, the poloxamer functions as follows: the hydrophobic part of the molecule is separated by hydrogen bonds, and the hydration layer envelops the poloxamer molecule.As the temperature rises, the hydrophilic chains disintegrate and the hydrogen bonds break. The process of polymer dehydration, which is linked to poloxamer gelation, results in hydrophobic association and an increase in chain friction and entanglement. Poloxamers are also known for their compatibility with other compounds, high solubilization capacity of various active

ingredients, and good characteristics for active ingredient prolonged release [14].Poloxamer 407 (P407, Pluronic F 127) is widely used because it allows the formation of colourless, transparent, and easily washable water gels, which are non-irritating to the skin and mucous membranes[15].

The use of thermosensitive liquid suppositories as cutting-edge drug delivery methods:

The creation of novel medications, novel drug formulations, or novel DDSs is one of the major developments in contemporary pharmacy. These solutions allow active ingredients to be delivered with the least number of adverse effects, in the desired location, at the appropriate time, and via the most convenient mode of administration.However, the process of finding novel synthetic medications is costly and time-consuming.One example is the manufacture of thermosensitive liquid suppositories.This dosage strategy modifies the pharmacokinetic properties of the drugs while retaining all the benefits of the rectal route. The publications that are currently accessible include research on thermosensitive liquid suppositories that can administer a variety of medications, such as antiemetic, anticancer, antihypertensive, and analgesics.

a) Analgesic Drugs:

Nonsteroidal anti-inflammatory medicines (NSAIDs), which are analgesics, are useful in treating a variety of illnesses, such as migraines, pyrexia, gout, muscular soreness, and dysmenorrhea and are used as opioid-sparing agents in certain acute trauma cases. NSAIDs are often sold as oral pills or capsules. There are also topical NSAIDs (e.g., gel, patch, topical solution) available. Parenteral administration of some NSAIDs is also an option (e.g., ibuprofen, ketorolac). Many drugs cannot be administrated in the above ways due to unfavourable properties, i.e., high first-pass effect, side effects, hydrophilic/lipophilic properties, etc.)[16].

Acetaminophen, often known as paracetamol, was the first medication to be used in a liquid suppository formulation that was thermosensitive. This medication has strong analgesic and antipyretic properties, but it has negligible anti-inflammatory properties [17]. In 1998, Choi and colleagues created the initial liquid suppository containing acetaminophen.A gelation temperature of 30–36 °C was used to manufacture novel in-situ gelling and mucoadhesive acetaminophen liquid suppositories with adequate bioadhesive force and gel strength. In order to impart temperature-sensitive gelation characteristics, P188 and P407 were used [18].

b) Anticancer Drugs:

Many administration methods are available for antineoplastic drugs, such as intramuscular, topical, intrathecal, intraperitoneal, intrapleural, intravenous, and intraperitoneal. Toxicology

also places limitations on chemotherapy. This toxicity could be reduced by using a suppository to administer drugs intrarectally. Using the thermosensitive liquid suppositories as a container for anti-cancer drugs is one potential use for them. This mostly relates to lower gastrointestinal tract tumor treatment [19].

5-fluorouracil (5-FU) is an antimetabolite drug that is commonly used to treat cancer, particularly colorectal cancer. This drug was turned into a thermosensitive liquid suppository by combining P407, a thermogelling agent, with pectin, a solubility-limiting agent, for rectal delivery. Additionally, the use of a mucoadhesive polymer such as carbopol 940 has altered the gelation temperature of P407. Yeo et al. used a different medication to create and test thermosensitive liquid suppositories [20].

c) Antiemetic Drugs:

Antiemetics are often administered orally or intravenously, yet difficulties with acute emesis or intrusive parenteral delivery can make patients less compliant.Moreover, vomiting is a common pediatric disease issue. For individuals who express trouble with oral vomiting therapy, the rectal route can serve as a substitute [21].

A metoclopramide (MET) in situ gelling device was created by Razek and associates as a successful rectal delivery route [22]. One useful antiemetic for preventing emesis in its different forms is MET. Due to its brief half-life (about 4 hours), frequent administration is necessary. P407 (20–25%) was used to make MET-loaded liquid suppositories with different concentrations of mucoadhesive polymers, such as HPMC, HEC, or PVP (0.5%, 1.5%, and 2.5%). [P407-MET-HPMC 25%:2%:2.5% w/w] was the thermosensitive liquid suppository with the highest mucoadhesive force, viscosity, and slowest drug release. The formulations that were developed had a gelation temperature that varied between 34.2 ± 0.121 °C. At room temperature, the formulation stays liquid, and when it reaches body warmth, it reversibly gels thermally [23].

d) Antihypertensive Drugs:

The majority of antihypertensive medications are taken orally. Exceptions include drugs that can be delivered sublingually and transdermally, as well as intravenous medications, which are usually utilized in emergencies or when the oral route is not acceptable [24]. Nonetheless, there are publications that describe how antihypertensive medications like carvedilol and propranolol are administered rectal [25]. Significantly, while still uncommon, this mode of administration can enhance the pharmacokinetics of antihypertensive medications [26].

A popular calcium channel blocker used to treat arrhythmia, angina pectoris, and hypertension is diltiazem hydrochloride. Keny and coworkers have developed and tested the in-situ gelling

and mucoadhesive liquid suppositories with diltiazem to enhance systemic drug absorption [27]. These formulations were prepared by adding mucoadhesive polymers at a concentration of 0.5% or 1.0% (carbopol 974P, Polyox WSR-301 (polyethylene oxide), HPMC, PCP, and PVP) to the formulation consisting of P407, P188 and diltiazem hydrochloride. The formulation containing P408/P188 in the ratio of 20/10% was selected as optimized for further study because it showed a gelation temperature in the range of 30–36 °C. The following was determined to be the mean average reduction in gelation temperature for all rectal gel formulations: PCP > Carbopol >Polyox WSR-301 > HPMC > PVP. It was shown that the kind and concentration of mucoadhesive polymers affected the gelation temperature. Furthermore, increasing the concentration of any of the used bioadhesive polymers from 0.5 to 1.0% resulted in a decrease in gelation temperature [28].

Method of preparation of Liquid suppositories:

Liquid suppositories were prepared bya cold method. The drug was dissolved in the calculated amount of distilled water at room temperature. The mucoadhesive polymers are incorporated in to drug solutions. Other excipients are slowly added to the previous solution with continuous agitation using a magnetic bar.The final weight was adjusted by cold distilled water.The mixturewas kept in the refrigerator at 4°C until a clear solution is obtained [29, 30, 31].

Evaluation parametersfor liquid suppositories:

a) Physical Examination:

Appearance: 5 ml of placebo formulation is taken into a clean and dry glass test tube and observed for clarity and presence of suspended particles if any against a black and white background. The color of a formulation is visually observed [32].

b) pH of liquid suppository:

The pH of suppository formulations is determined by using a digital pH meter [33].

c) Gelation temperature:

The gelation temperature of the medicated, mucoadhesive, and placebo liquid suppository is ascertained by the tube tilting method. For this, a 2 ml aliquot of liquid is transferred to a test tube which is sealed with aluminum foil, and the test tube is placed in a water bath at 4°C. The water bath's temperature will be raised by 1°C increments, and each new setting will be given 5

minutes to acclimate. Gelation temperature must be noted when the meniscusno longer moves upon tilting of the test tube through 90° [34].

d) Gel strength:

For gelation, a thermostat is set to 36.5°C and a 100ml glass measuring cylinder with 50g of the liquid suppository is placed inside. A 35g apparatus is placed on a gelled suppository to measure the gel strength. It is important to record how long it takes the apparatus to move 5cm into the bulk of gel [35].

e) Viscosity measurement:

A Brookfield viscometer or a cone and plate viscometer is used to measure the liquid suppository's viscosity. A sample solution of 0.5 ml was applied to the lower plate of the viscometer using glass rod. The viscosity is recorded using spindle no. 3 at a speed of 10 rpm with increased temperature [36].

f) Mucoadhesive strength:

A tissue specimen (a piece of tissue taken from the fundus of a sheep's rectum) is used to measure the mucoadhesive force of the liquid suppository used in in situ gels.

The pieces of tissue are stored in a simulated fluid having a pH of 6.8. For determination of mucoadhesive force, a section of tissue is secured (keeping the mucosal side out) to the upper side of a glass vial using double-sided adhesive tape. Every mucosal membrane that was seen had a diameter of 1.5 cm.The vials are kept for ten minutes at 37°C after equilibrating. A tissue slice-containing vial was fastened to the balance in one location, and another vial was placed on an adjustable pan at a different location. To the exposed surface of the tissue attached to the vial, a constant amount of 0.1 g gel is applied. The distance between the two vials is adjusted in such a way that the gel sample remains adhered to the mucosal membrane. Sufficient pressure is applied on both of the vials for 10 seconds to allow proper adhesion of gel to the mucosa. A constant weight is added to the pan (B) to the vial (C). The weight needed to separate the two vials and, consequently, the sample film between them is recorded. The following equation is used to calculate the mucoadhesive force, which is expressed as the detachment stress in dyne/cm2, based on the minimal weights required to separate the tissues from each formulation's surface [36].

Detachment stress (dynes/cm^2) = m X g/A

Where, m: weight added to the balance (gm)

g: acceleration of gravity

A: area of the tissue exposed ($\pi r2$)

g) Dissolution studies:

The USP II dissolution device was used to track the in vitro drug release investigations from the medicated liquid suppository and mucoadhesive liquid suppository. A non-absorbing thread is used to secure a 2g portion of the formulation inside a semi-permeable bag. Immersing the bag in a 500 ml pH 6.8 phosphate buffer at 37°C serves as the dissolution medium. It rotated at 100 revolutions per minute. Four milliliter aliquots are taken out and subjected to spectrophotometric analysis at a certain wavelength at predefined intervals [37,38].

CONCLUSION

The rectal route of administration is frequently a safe alternative for giving medication when the oral route is impractical due to unconsciousness, nausea, or vomiting. The most popular dose form for rectal medicine administration is a conventional solid suppository, but it gives patients a strange and uncomfortable feeling, which makes them refuse. The aforementioned problems with traditional solid suppositories can be resolved by developing a thermosensitive liquid suppository.

In comparison to solid suppositories, liquid suppositories are said to offer the greatest pharmacological composition.Liquid suppositories are a useful tool in treating a variety of medical diseases because they may be tailored to give controlled release, site-specific targeting, and improved patient compliance. Their adaptability to hydrophilic and hydrophobic medications increases the range of applications for which they can be used. This review study suggests more investigation into the previously stated fields.

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