Hydrogel Matrix Diffusion Technology: Development of Controlled Release Formulation Aiming for Enhanced Adherence

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Abstract

Hydrogels or hydrated matricesare water-based three-dimensional systems with numerous hydrophilic groups. The highly porous hydrogels swell on exposure to water in the gastrointestinal tract creating a mesh-like structure of the polymer cross-links, entrapping the drug particles inside that matrix. Subsequently, the embedded drug particles diffuse through the swollen gel-like layer creating a controlled impediment to drug release. The zones of the dissolved and un-dissolved drug are parted by two sides from the swollen gel region, namely the diffusion front and the erosion front. Drug release can occur by diffusion, erosion, or both. Thus, drug release is modulated by the hydrogel barrier enabling controlled release. This Hydrogel Matrix Diffusion Technology (HMDT) offers dimensional and temporal regulation of drug release patterns. Carbopol polymers also known as smart gels are usually used to manufacture stimuli-responsive (pH or temperature) hydrogels enabling their utilization across therapy areas. Given their several conformable parameters that permit the controlled delivery of various therapeutic agents, hydrogels are exceptional contenders for oral drug delivery. HMDT can help improve adherence by reducing the dosing frequency/pill burden, thereby improving clinical outcomes. This is particularly critical for chronic diseases like diabetes, chronic stable angina, heart failure, hypertension, and several others. There is adequate clinical evidence for example the PROFICIENT study with Ivabradine showing similar clinical effectiveness with a once-daily regimen as multiple-dose regimenswith improved treatment compliance.

Keywords: hydrogel matrix diffusion technology, once-daily regimen, chronic diseases, adherence

Introduction

Need for Controlled Drug Delivery Systems

Drug development predominantly aims at formulating drug delivery systems to avert an active therapeutic agent from premature degradation, improve drug effectiveness and reduce side effects. Preferably, controlled release systems maintain the required drug levels within a therapeutic window over a prolonged duration, reducing dosage and frequency of administration. [1, 2] Oral route of drug administration is preferred for several disease conditions, especially chronic diseases to improve adherence. [3, 4] Patients' adherence to their prescribed therapy is critical in the optimal management of chronic disease conditions and attaining clinical goals. People who suffer from chronic and multiple comorbidities require multiple drug regimens or polypharmacy. Adherence is predominantly challenging in adults prescribed polypharmacy; both being inversely proportional to each other. A recent study has reported that in developed countries, adherence among patients suffering from chronic diseases is merely 50%. Adherence is, therefore, a prevalent issue of grave concern. Poor medication adherence severely impairs the efficacy of prescribed therapy elevating the risk of associated morbidity and mortality.

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Traditional oral formulations used for drug administration commonly necessitate higher dosages and/or multiple doses to attain the desired clinical benefit. Patient adherence and consequently efficacy is influenced by the dosage and its frequency. The adverse effect profile and the convenience of a particular treatment are associated with both these factors. Further in certain instances,the oral route of drug administration is also limited by poor bioavailability, which in turn may enhance the need for higher and frequent dosing. [5]Various controlled drug delivery systems such as nanoparticles, liposomes, and hydrogels have evolved in the last decade. These novel drug delivery systems regulate the drug release ensuring improved bioavailability. Consequently, similar efficacy can be achieved with reduced dosing frequency, thereby reducing the pill burden for patients.

Hydrogel Matrix Diffusion Technology (HMDT)

Characteristics

Hydrogels or hydrated matrix are water-based systems consisting of a crosslinked polymer grid. These three-dimensional structures with numerous hydrophilic groups (–OH, $–SO_3H$, –COOH, $–NH_2$) can absorb and detain copious amounts of water with no decline in losing structural stability.[6,7,8] Owing to the stability, Hydrogels are capable of retaining absorbed solutions within theirnetwork, even in the presence of an external force.[9] The crosslinking retains the hydrogel structure without getting dissolved in any fluid. [10] Due to their water-based nature, hydrogels are compatible with most tissues and encapsulate all hydrophilic drugs. The cross-linked polymer prevents untimely degradation by physiological enzymes. This system offers dimensional and temporal regulation of drug release patterns.

Mechanism of Drug Release in HMDT

The highly porous hydrogels swell on exposure to water in the gastrointestinal tract creating a mesh-like structure of the polymer cross-links, entrapping the drug particles inside that matrix. Subsequently, the embedded drug particles diffuse through the swollen gel-like layer creating a controlled impediment to drug release. [11] The zones of the dissolved and un-dissolved drug are parted by two sides from the swollen gel region, namely the diffusion front and the erosion front.[11, 12] Drug release can occur by diffusion (soluble part), erosion (insoluble part), or both.[13] Thus, drug release is modulated by the hydrogel barrier enabling controlled release.

Types of Polymers Used in HMDT: Focus on Carbopol Polymers

The route of delivery of a certain drug dictates the choice of physical aspects such as the size of the hydrogel which can be formed into virtually any size, primarily macrogels, microgels (dimensions in μm), and nanogels (dimensions in nm) or scaffolds as the matrix.[14] Microgels generally measuring 10 μm are used for oral administration. Crosslinking is either physical or chemical. In physical hydrogels, crosslinking occurs due to noncovalent bonding among the polar groups ofthe polymer, while, in chemical hydrogels, crosslinking occurs through covalent bonds.[15] Hydrogels are considered a potential candidate for drug delivery with reversible responses to various stimuli such as pH, temperature, etc.[15]

The most scrutinized hydrogels among stimuli-responsive hydrogels are pH-sensitive hydrogels. These quick alterations displayed by such hydrogels are contraction and swelling following exposure to a certain stimulus, causing the shift to the volume phase.

Carbopol polymers also known as smart gelsare usually used to manufacture stimuli-responsive hydrogels that result in modifications of swelling manner on exposure to external stimuli such as pH or temperature.[16, 17, 18, 19] Carbopol is particularly considered a suitable candidate for controlled drug-delivery systems. Carbopol swells maximum in alkaline pH and therefore transports the maximum drug at alkaline pH.[20] Acrylic acid is apH-sensitive polymer used in stimuli-sensitive polymeric carrier systems like Carbopol. [21] These features enable the utilization of hydrogels across therapy areas.

Thus, hydrogels are exceptional contenders for oral drug delivery, given their several conformable parameters that permit the controlled delivery of various therapeutic agents.

Benefits of HMDT-based formulations

Apart from diabetes, in India the burden of chronic diseases like heart failure and angina is huge. The incidence of non-adherence is also very common in patients with cardiovascular diseases like HF. [22] It has been estimated that 9% of cardiovascular events can be attributed to non-adherence.[23] The complexity of dosing regimens has been identified as one of the factors contributing to non-adherence.[23] The REACH registry found that non-adherence was nearly 70% of Asians. [24] Inadequate adherence leads to an increased risk of HF exacerbations, reduced physical activity, and an elevated risk for the hospital admission. Non-adherence forms a huge public health threat since it can affect dai-

ly patient management, due to unwarranted therapeutic escalation with the potential for increased hospitalizations, morbidity, and mortality.[25] Several meta-analyses have confirmed that once-daily controlled-release formulations lower the pill burden and therefore lead to a significant increase in adherence.[26]Dosing regimens with once-daily administration were associated with a significant 56% reduction in non-adherence to drug therapy in patients with chronic cardiovascular diseases.[23] In a study comparing once-daily versus twice-daily formulations in patients with angina, a significantly greater decrease in the mean weekly number of angina episodes was noted. Also, the need for rescue medications was decreased in the once-daily group.[27] The PROFICIENT study with Ivabradine has shown that the clinical effectiveness of a once-daily regimen is similar to multiple-dose regimenswith improved treatment compliance.[28] Thus, the development of innovative drug delivery systems like HMDT can help improve adherence by reducing the dosing frequency/pill burden, thereby improving clinical outcomes. This is particularly critical for chronic diseases like diabetes, chronic stable angina, heart failure, hypertension, and several others.

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