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Smart materials: *in situ* gel-forming systems for nasal delivery

Christina Karavasili and Dimitrios G. Fatouros

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Department of Pharmaceutical Technology, School of Pharmacy, Aristotle University of Thessaloniki, 54124, Greece

In the last decade *in situ* gelling systems have emerged as a novel approach in intranasal delivery of therapeutics, capturing the interest of scientific community. Considerable advances have been currently made in the development of novel formulations containing both natural and synthetic polymers. In this paper we present recent developments on *in situ* gelling systems for nasal delivery, highlighting the mechanisms that govern their formation.

Introduction

Q2 Nasal drug delivery has been attracting significant research interest in the last years, as route of multi-variant targeting, employing topical drug administration, systemic drug delivery, as well as brain drug targeting. The nasal cavity has been emerged as an attractive route of administration, from drug molecules to peptides and protein drugs and vaccines, resulting to the successful launch of a plethora of marketed nasal formulations [1].

Oral drug delivery, the most common route of administration, is simpler, improves patient compliance and comfort. Nevertheless, many pharmaceutically active compounds, especially macromolecules, commonly confront the drawback of low bioavailability, ascribed to extended first-pass hepatic metabolism, low permeability across gastrointestinal tract and chemical/proteolytic degradation [2].

The nasal route has been considered as a viable and efficacious alternative route to tackle these obstacles. Circumvention of the extended first pass metabolism, avoidance of the harsh environment of the gastrointestinal tract, enhanced pharmacokinetic profiles for the lipophilic molecules deriving from the favorable anatomical characteristics of nasal epithelium, brain targeting through the olfactory region and patient compliance can be considered the main advantages of this route of administration [3].

However, the limited capacity of the nasal cavity, the low membrane permeability of hydrophilic molecules, along with the rapid mucociliary clearance effect, constitute the main rate-limiting factors for nasal drug absorption. For that reason, research majorly oriented toward the exploitation of bioadhesive agents and/or permeation enhancers for the development of delivery systems able to extend formulation's residency in the nasal cavity, further improving drug absorption and bioavailability of polar compounds [3], with the recent focus on smart stimulus-responsive systems.

Intelligent drug delivery systems responding mainly to physiological stimuli have emerged as an innovative approach for the delivery of therapeutic agents. Owing to their properties, *in situ* gelling formulations have the ability to undergo a phase transition; a solution to gel formation, triggered either by physiological factors upon intranasal administration (e.g. temperature, ion concentration, water content). As a result, in actual usage these dosage forms can be easily administered as solutions, assuring accuracy in the administered dose, whereas gel formation upon contact with the nasal epithelium is of utter importance to ascertain sufficient contact time and thus improved bioavailability.

Thermo-responsive systems

The concept involves the development of mucoadhesive formulations comprising of polymers which exhibit temperature-triggered sol-to gel transitions in the range of 25–37 °C. Below or above this temperature range, early or late gelation might occur, either hindering ease of handling or inducing liquid formulation's leakage in the outer region of the nostrils.

Synthetic thermo-responsive polymers

A commonly used mucoadhesive polymer is Poloxamer 407, which is known to bear thermosensitive properties. Poloxamer 407 undergoes micellization in a concentration and temperature-dependent

Corresponding author: Fatouros, D.G. (dfatouro@pharm.auth.gr)

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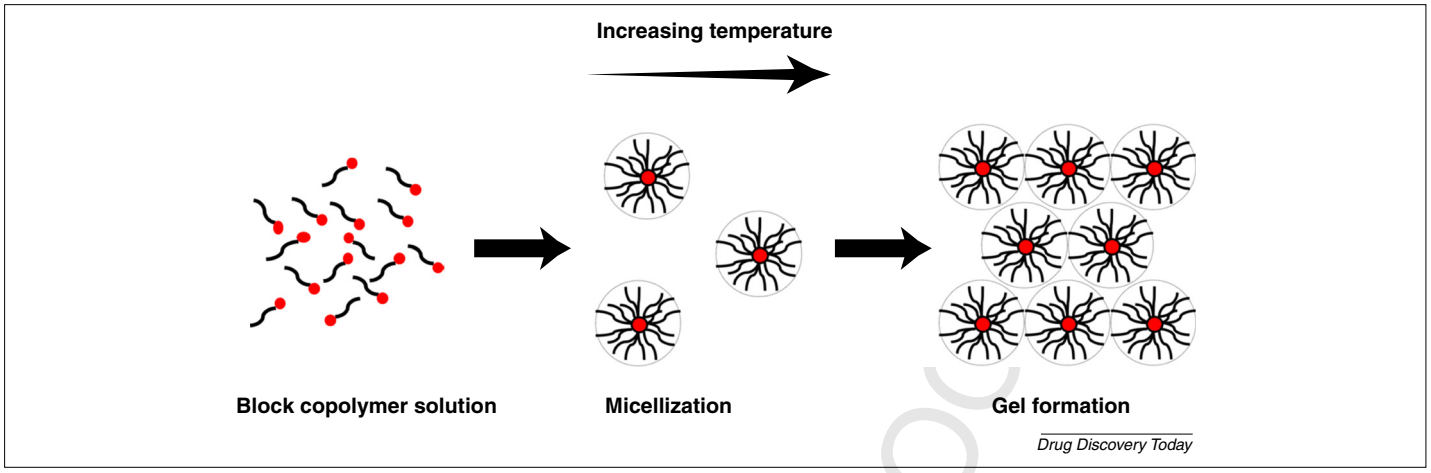

FIGURE 1

Schematic illustration of the mechanism of *in situ* gelation of a thermo-responsive polymer as a function of temperature. Upon temperature rise, polymer desolvation accompanied with side chain conformational changes, result in displacement of the hydrating water molecules, modifications of micelles orientation and consequently gel formation.

manner, shifting to gel formation by micellar packing (Fig. 1). The underlying mechanism of gel formation, as a function of temperature, suggests polymer desolvation accompanied with side chain conformational changes, resulting in displacement of the hydrating water molecules and modifications of micelles orientation [4]. The thermo-responsive properties of Poloxamer 407 have been extensively exploited in the development of *in situ* nasal gels in combination with mucoadhesives, essential for the prolongation of formulation's residency in the nasal cavity.

Driven by the low oral bioavailability of sumatriptan (15%), used in the treatment of migraine, Majithiya *et al.* [5] developed an *in situ* gel by utilizing Poloxamer 407 and Carbopol 934P. The gel exhibited a $T_{sol-gel}$ temperature ranging from 23.9 °C to 29 °C with decreasing Carbopol's concentration, with the suppression effect on gelation temperature as a function of polymer's concentration, partly associated to the subsequent increase in viscosity after polymer dissolution. The gel formulation containing 0.3% Carbopol exhibited favorable mucoadhesive properties and significantly enhanced the *in vitro* drug permeability, compared to the solution form, inducing no structural defects on nasal membrane.

In an attempt to confront the extreme variations in the oral bioavailability of metoclopramide hydrochloride (ranging from 32% to 98%), the patient incompliance of parenteral and rectal drug administration and drug's bitter taste perception, Zaki *et al.* [6] co-formulated the antiemetic compound with Poloxamer 407, polyethylene glycol (PEG) and an array of mucoadhesive polymers. The results demonstrated that the presence of mucoadhesives increased the viscosity of the gels, thus shifting $T_{sol-gel}$ temperature toward lower values and delayed metoclopramide release rate. *In vivo* mucociliary transport time (MTT) measurements indicated prolonged retention of the carbopol containing *in situ* gel in the rat nasal cavity. Optimized formulation, comprising 0.5% Carbopol, achieved higher serum drug levels and a shorter T_{max}, compared to the oral drug solution, also retaining mucosal integrity for extended periods of time after *in vivo* administration.

The limitations in the brain uptake of hydrophilic molecules, compelled Gabal *et al.* to formulate the anti-parkinsonian ropinirole hydrochloride in nanostructured lipid carriers (anionic and cationic), integrated in Poloxamer 188 *in situ* gels [7]. The lack of any toxic histopathological findings confirmed the safety of the systems. Both gels (anionic $T_{sol-gel}$: 34 °C, cationic $T_{sol-gel}$: 33.4 °C) exhibited exceptionally enhanced absolute bioavailability values, when compared to plain ropinirole solution, achieving drug targeting to the brain mainly via the olfactory route.

An array of in *situ gels* of Poloxamer 407 and Poloxamer 188 co-formulated with Carbopol 934, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, chitosan and diphtheria toxoid were evaluated for their adjuvanticity after intranasal administration [8]. The intranasal administration of selective formulations, based on their mucoadhesive and *in vitro* release properties, was found to be inadequate to produce systemic immune response. On the other hand, subcutaneous vaccination accompanied by intranasal administration of the chitosan containing *in situ* gel, resulted in increased neutralizing antibody titers, facilitating partial protection against diphtheria toxoid.

The neuronal uptake for the nose-to-brain delivery of ^{32}P-siRNA dendriplexes was evaluated by Perez *et al.* [9], in order to circumvent the blood brain barrier. Thermally triggered *in situ* gels comprised of Poloxamer 407 and two mucoadhesives, namely Carbopol 934P and chitosan, were developed. The results demonstrated that the Carbopol containing formulations displayed optimum rheological properties, exhibiting a $T_{sol-gel}$ at 23 °C, compared to their congener with chitosan, with the later hindering the release of the siRNA dendriplexes. Histological studies revealed the absence of any epithelial toxicity upon application of the gel formulation, achieving higher levels of radioactivity to the brain, compared to intravenous and intranasal-in-buffer administration. Further studies are also mandatory to substantiate the silencing effect of dendriplexes *in vivo*.

In an effort to regulate the $T_{sol-gel}$ of an *in situ* gel at 33.5 °C, Poloxamer 407 was co-formulated with different amounts of Poloxamer 188 and PEG 6000 and paenolol, extracted from the root bark of *Paeonia suffruticosa* bearing analgesic, antioxidant and anti-inflammatory properties [10]. Authors reported an optimum composition of 22% Poloxamer 407, to enable increased micellar entanglement, 2% Poloxamer 188 and 2% PEG 6000, as $T_{sol-gel}$

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