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Brain targeted rivastigmine mucoadhesive thermosensitive *In situ* gel: Optimization, *in vitro* evaluation, radiolabeling, *in vivo* pharmacokinetics and biodistribution

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ABSTRACT

The purpose of our investigation was to promote the bioavailability and the brain delivery of rivastigmine tartarate (RV) through optimization of mucoadhesive thermosensitive *in situ* gel via intranasal (IN) route. The mucoadhesive *in situ* gels were developed using pluronic F127 (PF127) as thermogelling agent and different mucoadhesive polymers. A full factorial design was implemented to study the influence of three factors; pluronic type at two levels (PF127, PF127/PF68), mucoadhesive polymer type at four levels (HPMC, Chitosan, Carbopol 934 and NaCMC) and mucoadhesive polymer concentration at two levels (0.5 and 1%w/v). The studied responses were sol-gel temperature, consistency, gel strength, adhesion work and $T_{50\%}$ of drug release. In vivo pharmacokinetic and biodistribution studies of the selected formula were investigated using radiolabeling approach using normal albino mice. The optimal RV *in situ* gel (PF127 and 1% Carbopol 934) showed significant transnasal permeation (84%) which was reflected in better distribution to the brain (0.54 %ID/g), when compared to RV IN solution (0.16 %ID/g) and RV IV intravenous solution (0.15 %ID/g). In conclusion, the investigated results showed the potential use of mucoadhesive *in situ* gel as a promising system for brain targeting of RV via the transnasal delivery system.

1. Introduction

In the past years, nasal delivery of drugs has been acknowledged as a competitor administration route over other traditional routes. The nasal dosage form achieves a noticeable patient compliance as patient can painlessly administer the drug by himself [1]. In addition to the high absorption of the drugs administrated intranasally, owing to the high membrane permeability and rich vasculature in the nasal cavity, it can also speed up the intended therapeutic action [2]. Furthermore, the nasal route offers further benefits over the oral route, especially for those drugs that have low oral bioavailability due to intensive hepatic first-pass metabolism, enzyme degradation and/or pH instability in GIT [3,4].

Nowadays, the IN route has gained more interest to target drugs to the cerebro-spinal fluid and brain. IN formulations containing drugs for the treatment and curing of Parkinson's disease [5], Alzheimer's disease [6] and depression [7] have been introduced and their therapeutic efficiency over conventional oral dosage form has been verified.

Rivastigmine tartrate (RV) is the recommended drug for treatment of Alzheimer's disease. This disease is characterized by progressive memory dysfunction due to significant deficiency of acetylcholine in the brain [8]. RV as a reversible cholinesterase inhibitor enhances acetylcholine levels in the brain by inhibiting both acetylcholinesterase and butyrylcholinesterase enzymes present in the central nervous system [9,10]. RV is accessible in the market as solution, transdermal patches and capsule. It has been revealed to suffer from extensive first-pass metabolism, resulting in a low bioavailability of about 35% and short elimination half-life of 90 min, imposing frequent administration, which may cause an accumulation of the drug cholinergic side effects [11–13].

Nasal *in situ* gelation can be accomplished by different techniques; one of them is using thermosensitive polymers where a gel is formed

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Abbreviations

RV	Rivastigmine tartarate
HPMC	Hydroxypropyl methyl cellulose
CS	Chitosan
CP 934	Carbopol 934
NaCMC	sodium carboxy methyl cellulose
PF127	Pluronic F-127
PF68	Pluronic F-68
SNES	simulated nasal electrolyte solution
$T_{sol-gel}$	sol-gel transition temperatures
PPO	polypropylene oxide
PEO	polyethylene oxide
EAEA	Egyptian Atomic Energy Authority
IN	intranasal
IV	intravenous
PC	paper chromatography
DTE %	drug-targeting efficiency
DTP %	direct nose-to-brain transport
NaI	sodium iodide
^{99m}Tc	Technetium-99 m

upon the administration by sensing the physiological nasal temperature. Pluronics, having different grades, are characterized by good thermosensitive gelling properties, low irritation and toxicity, high water solubility, good drug release characteristics and adequate polymer-polymer compatibility [14,15]. However, low residence time at the site of the administration may represent an obstacle in this route. This is owed to nasal rapid mucociliary clearance which in turn limits the time necessary for drug absorption [16]. Consequently, in the design of intranasal formulations, one must improve the residence time by using polymers with mucoadhesive properties that are particularly helpful in providing intimate contact between the dosage form and the nasal mucosa and hence maximizing the likelihoods of the drug absorption. Therefore, the objective of this study is to formulate RV mucoadhesive *in situ* gel to enhance drug bioavailability and thus increase its brain concentration.

2. Materials and methods

2.1. Materials

Rivastigmine tartarate (RV) was kindly supplied from EVA Pharma Egypt. Pluronic F127 (PF127, approx. m.wt. 12,000), Pluronic F68 (PF68), Sodium carboxymethyl cellulose (NaCMC, 400–800 m Pas., 2% in aqueous solution at 25 °C), and Hydroxypropylmethyl Cellulose (HPMC, 2% aqueous solution at 40–60 Cp, 2% in aqueous solution at 25 °C) Sigma chemical Co., St. Louis, MO, USA. Carbopol 934 (CP 934, m.wt. 3 × 106), BF Goorich, USA. Chitosan (CS, low molecular weight, 75–85% degree of acetylation) Titan Biotech Limited, India. Acetonitrile and acetic acid, Prolabo, France. Sodium chloride, potassium chloride and calcium chloride dihydrate, ADWIC Co., Egyp, Stannous Chloride dihydrate ($SnCl_2.2H_2O$, Sigma-Aldrich), Technetium-99 m (^{99m}Tc) was eluted in the form of $^{99m}TcO_4^-$ from ^{99}Mo/^{99m}Tc generator, Radioisotope Production Facility, EAEA, Egypt.

2.2. Methods

2.2.1. Preparation of RV thermosensitive mucoadhesive gels

$2^2 \times 4^1$ full factorial design was implemented in the preparation of RV thermosensitive mucoadhesive gels using three different factors, i.e., pluronic type at two levels (PF127, PF127/PF68), mucoadhesive polymer type at four levels (HPMC, CS, CP 934 and NaCMC) and the concentration of mucoadhesive polymers at two levels (0.5 and 1% w/v).

The *in situ* gels were prepared using the cold method described by Choi et al. [17] with minor modification. The calculated amounts of the drug and the mucoadhesive polymer were stirred in de-ionized water or 1% v/v acetic acid solution in case of CS using a magnetic stirrer. Afterwards, this dispersion was stored in refrigerator to cool down to 4 °C. The calculated amounts of PF127 with or without PF68 were added to the cold dispersion and stirred continuously using a magnetic stirrer at 1200 RPM. The dispersions were again stored in refrigerator overnight. The composition of the prepared RV mucoadhesive *in situ* gel is shown in Table 1.

2.2.2. Measurement of the sol–gel transition temperatures ($T_{sol-gel}$)

The $T_{sol-gel}$ of the prepared formulations was measured as designated by Gilbert et al. and Vadnere et al. [18,19]. Concisely, 2 ml of RV *in situ gel* was transferred to a sealed test tube placed in a water bath at 15 °C. The temperature of the bath was increased gradually of 2 °C at the beginning, then 0.5 °C in *sol–gel* transition range with equilibration at each temperature. The gelation temperature was recorded at the temperature where the gel would no longer move upon tilting the test tube 90° (measured in triplicate).

2.2.3. Rheological behavior

The rheological properties of RV *in situ* gel were studied using Brookfield Viscometer, type DV III at three different temperatures namely; 4 ± 0.1 °C, 25 ± 0.1 °C and 35 ± 0.1 °C using spindle 52 within 10–250 rpm. The shear rate (γ) in s^{-1} and the viscosity (η) in centipoises (cps) were determined and fitted to the power law model equation [20]:

$$\eta = k\gamma^{n-1} \quad (1)$$

The flow index (n) and the consistency index (k) of each formulation were estimated. If ($n = 1$) this reveals Newtonian behavior while if ($n < 1$), this relates to shear thinning flow. The lower the (n) value the more shear thinning of the formulation [21,22].

Table 1
The composition of RV*in situ* gels.

Formula NO	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Rivastigmine(mg)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
PF127*	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
PF68*	–	–	–	–	–	–	–	–	10	10	10	10	10	10	10	10
HPMC*	0.5	1	–	–	–	–	–	–	0.5	1	–	–	–	–	–	–
Chitosan*	–	–	0.5	1	–	–	–	–	–	–	0.5	1	–	–	–	–
CP934*	–	–	–	–	0.5	1	–	–	–	–	–	–	0.5	1	–	–
NaCMC*	–	–	–	–	–	–	0.5	1	–	–	–	–	–	–	0.5	1

*used in %, w/v.