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Original Article

Preparation and Evaluation of a Thermo-adhesive Gel Formula Containing Pioglitazone as a Drug Carrier to the Brain Through the Nasal Cavity

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ABSTRACT

Background: Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, has demonstrated potential in managing Alzheimer's disease (AD); however, its oral administration is limited by systemic side effects such as cardiovascular risks and hepatotoxicity. This study aims to formulate and evaluate a thermo-adhesive intranasal gel containing pioglitazone, utilizing Poloxamer 407 and Carbomer, as a targeted drug delivery system for AD.

Methods: A series of gel formulations was prepared and assessed for gelling capacity, homogeneity, pH, and stability. The solubility of pioglitazone in various solvents was tested, and the optimal thermo-adhesive gel was selected based on gelation at physiological temperature (37°C–39°C).

Results: The formulation containing 3 g Poloxamer 407 and 0.8 mg Carbomer successfully transitioned into a gel at body temperature and maintained physical stability over 2 months under accelerated conditions. The pH remained within the acceptable intranasal range (5.7–6.0), and no visual or olfactory changes were observed.

Conclusions: The developed thermo-adhesive intranasal gel offers a promising alternative to oral pioglitazone delivery for AD, with the potential for enhanced Central Nervous System (CNS) targeting and reduced systemic side effects. Further toxicity and in vivo efficacy studies are warranted to confirm safety and therapeutic value.

Key words: Thermo-adhesive gels, pioglitazone, Alzheimer's disease

INTRODUCTION

Alzheimer's disease (AD), a progressive neurodegenerative condition, is a leading cause of dementia worldwide. Characterized by memory loss, cognitive decline, and behavioral disturbances, AD imposes a significant burden on patients, caregivers, and healthcare systems. Current pharmacological treatments, including acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor (NMDA) receptor antagonists, provide only modest symptomatic relief without altering disease progression. [1] The incidence

of neurological diseases increases significantly with age, from 40.51 per 100,000 individuals in the 40 to 49 years age group to 1,902.98 per 100,000 individuals aged 80 years and above. [2] AD, one of the most prevalent neurodegenerative diseases, is characterized by progressive cognitive decline.

Recent research has explored the potential of pioglitazone, a proliferator-activated receptor gamma (PPARγ) agonist traditionally used for type 2 diabetes, in modulating neuroinflammation and improving insulin sensitivity in the brain. Preclinical studies suggest that pioglitazone may delay cognitive decline in AD. However, its clinical use is limited due to adverse effects such as bladder cancer risk, edema, and hepatotoxicity when administered orally. [3] To address these limitations, alternative drug delivery approaches are being developed. Intranasal delivery is gaining attention due to its non-invasive nature and ability to bypass the blood-brain barrier via the olfactory and trigeminal pathways, allowing direct access to the central nervous system. [4] Thermosensitive gels, particularly those based on Poloxamer 407, exhibit sol-to-gel transitions at body temperature, making them ideal for intranasal administration. When combined with mucoadhesive agents like Carbomer, these formulations can enhance residence time and drug absorption.

Therefore, this study aims to develop and evaluate a Poloxamer 407-based thermo-adhesive intranasal gel loaded with pioglitazone, intended for the management of Alzheimer's disease. The study further investigates its physicochemical properties, stability, and preliminary safety to assess its potential as a targeted CNS delivery system.

MATERIALS AND METHODS

The study utilized Poloxamer 407, Carbomer 940, pioglitazone, and excipients, including polyethylene glycol (PEG) and propylene glycol (PG), sourced from local institutions and pharmaceutical industries in Yemen. The experimental setup included water baths, thermometers, hot stirrer plates, balances, pipettes, beakers, cylinders, and magnetic stirrers for gel formulation and characterization.

Study area

This project was conducted in the laboratories of Al-Nasser University, Faculty of Medical Sciences, Department of Pharmacy. The stability study of the formulated gel was performed at Global Pharma for Pharmaceutical Industry, Sana'a, Yemen.

Formation of an ordinary gel to learn how to form an ordinary gel

Seventy milliliters of water were added to a 100 mL beaker, which was then placed in a water bath. Gradually, 0.3 mg of Carbomer (mucoadhesive) was added with continuous stirring in a single direction. Once the Carbomer was fully dissolved, drops of sodium hydroxide (NaOH) were added to the mixture to initiate the gel formation process. [5]

Formation of thermo-adhesive gel using poloxamer 407 (P407)

A 100 mL beaker was prepared, and the desired amount of Poloxamer 407 was added to it. The beaker was placed on a magnetic stirrer on a hot plate to facilitate the dissolution of Poloxamer 407. Once fully dissolved, a sufficient amount of Carbomer was added through a sieve (**Figure 1**). After ensuring complete dissolution of the Carbomer, the temperature was increased to 39°C in the water bath (**Figure 2**), and a thermometer was used to monitor the temperature of the formulation. Finally, when the Poloxamer transitioned into a gel, the result was recorded. [6,7]

Ways to dissolve pioglitazone

Initially, diluted hydrochloric acid (HCl) was used to dissolve the pioglitazone; however, it did not dissolve in the hydrochloric acid (**Figure 3**). Subsequently, sodium alginate mixed with water was attempted to dissolve the pioglitazone, but unfortunately, it also failed to dissolve (**Figure 4**). [8] Finally, PEG and PG were used to dissolve the pioglitazone, and this method successfully dissolved the pioglitazone (**Figure 5**). [9]

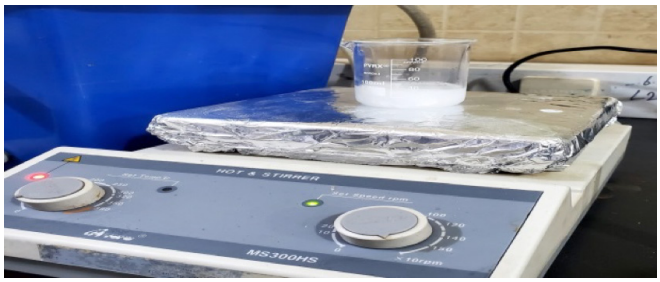

Figure 1: The process of dissolving poloxamer 407 (P407) using a hot stirrer plate.

Figure 2: The process of observing the change of poloxamer 407 (P407) to gel at body temperature using a water bath.

Figure 3: Pioglitazone was not dissolved in the diluted HCL.

Formulations, compositions, and evaluations

Compositions of thermo-adhesive gel (poloxamer 407) formulations as a nasal spray (Table 1)

Compositions of a thermo-adhesive nasal spray containing pioglitazone and its solvents with different amounts of carbomer (Table 2)

Evaluations of formulations

Organoleptic evaluation

The obtained nasal spray was evaluated for its organoleptic properties, such as color, odor, and state. [10]

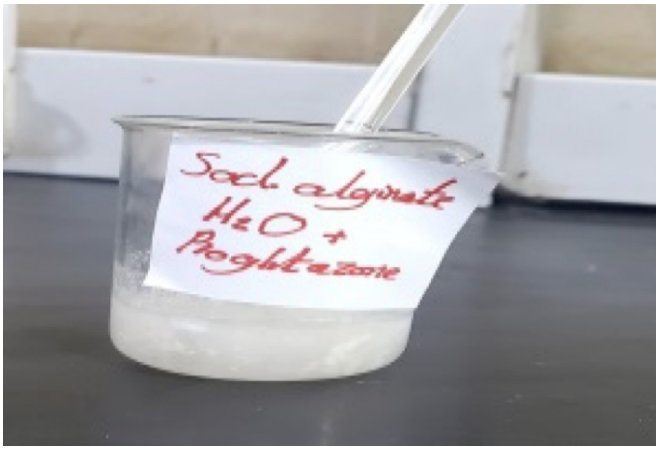

Figure 4: Pioglitazone was not dissolved in sodium alginate and water.

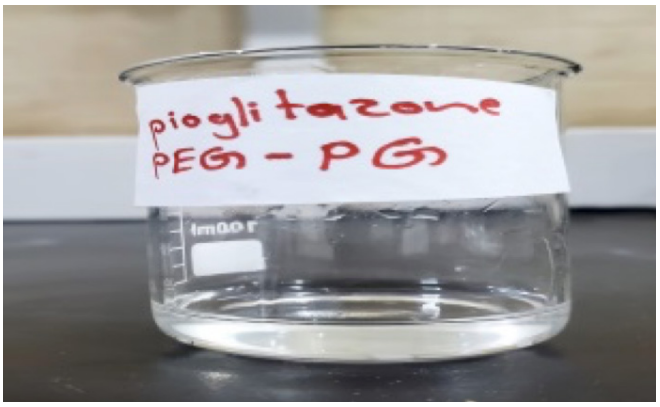

Figure 5: Pioglitazone was dissolved in polyethylene glycol (PEG) and propylene glycol (PG).

pH of the nasal spray

The pH meter was calibrated using a standard buffer solution. The pH of the nasal spray was measured using a calibrated pH meter. [10,11]

Homogeneity

The formulations were tested for homogeneity by visual appearance. [10]

Accelerated stability study for thermo-adhesive gel containing pioglitazone as a nasal spray

The stability study of the formula was carried out according to ICH guidelines by storing the formula in a stability chamber at 40 ± 2°C\75 ± 5% Relative Humidity (RH) for 2 months. The effects of temperature, relative humidity, and time on the physical and chemical characteristics of thermo-adhesive gel containing pioglitazone as a nasal spray were evaluated to assess the stability of the prepared formula. [12]

RESULTS AND DISCUSSION

Results to obtain the desired concentration of poloxamer 407 (thermo-adhesive gel; Table 3)

Six formulations (**Figure 6**) are performed to gain the correct formula using different concentrations of poloxamer 407, and physical evaluation (gelling temperature) is performed for each one alone, as illustrated in **Table 4**.

From **Table 3** above, all five formulations do not form gel at body temperature or above (37°C–39°C) except formula number 3 (**Figure 7**), which forms gel at 37°C to 39°C. So, formula number three is a suitable formula for pioglitazone.

Results of thermo-adhesive gel (formula number 3) containing pioglitazone

Five formulations (**Figure 8**) are performed to obtain the desired formula of thermo-adhesive gel containing pioglitazone using different amounts of carbomer, as illustrated in **Table 2**.

From **Table 4** above, all three formulations do not form gel at body temperature or above (37°C–39°C) except formula number 4 (**Figure 9**), which forms gel at 37°C to 39°C. So, formula number four is a suitable formula that performs the desired thermos-adhesive gel containing pioglitazone.

Results of stability study of thermo-adhesive gel containing pioglitazone

The result of the accelerated stability study for the optimized formula during 2 months is summarized in **Table 5** below.

Table 1: Compositions of each thermo-adhesive gel formula:

Compositions	Formula					
	F1	F2	F3	F4	F5	F6
Poloxamer	2.5 g	2.75 g	3 g	3.25 g	3.5 g	3.75 g
Carbomer	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Distal Water (D.W.)	25 mL	25 mL	25 mL	25 mL	25 mL	25 mL

From the above results in **Table 5**, an accelerated stability study has been conducted for the first 2 months, and the study results show that the physical properties after 1 month and 2 months at high-stress conditions (40°C and 75% RH) show acceptable results and no changes compared to the results at zero time. Moreover, there are similar studies that show similar results to those obtained in this study. For instance, an in-situ gel preparation containing moxifloxacin was prepared using poloxamers as a drug delivery system for the treatment of periodontal diseases. [13]

Preliminary toxicity assessment

Although comprehensive animal testing was beyond the scope of this study, preliminary toxicity evaluation was carried out using pH measurement, viscosity, and organoleptic properties to ensure suitability for intranasal administration. All formulations exhibited pH values between 5.7 and 6, which falls within the acceptable range for nasal mucosa and suggests good tolerability. No irritation, discoloration, or odor changes were observed during accelerated stability studies. Further in vivo and cytotoxicity studies are required to confirm the safety profile of the developed formulation.

CONCLUSIONS

AD results in significant cognitive and motor impairments. While pioglitazone has shown the potential to slow disease progression, its oral administration is associated with adverse effects. The thermo-adhesive gel formulation with Poloxamer 407 and pioglitazone presents a promising alternative delivery method for AD treatment, potentially offering a safer and more effective option.

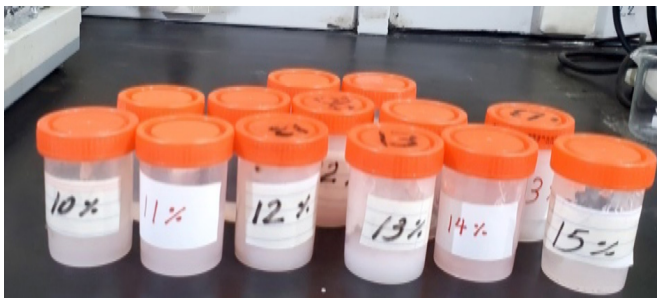

Figure 6: The used formulations to obtain the desired concentration of poloxamer 407 (thermo-adhesive gel).

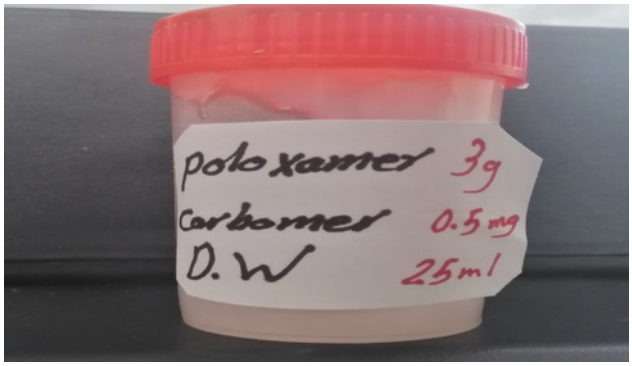

Figure 7: The desired thermo-adhesive gel formula.

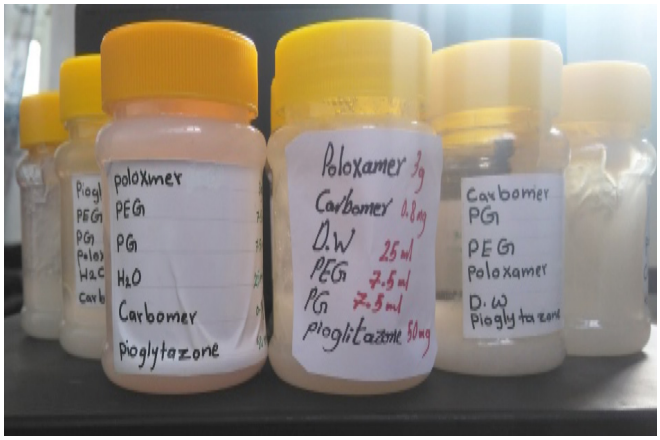

Figure 8: Results of thermo-adhesive gel (formula number three) containing pioglitazone.

Table 2: Compositions of each formula of thermo-adhesive gel containing pioglitazone:

Compositions	Formula			
	F1	F2	F3	F4
Poloxamer	3 g	3g	3 g	3 g
Carbomer	0.5 mg	0.6 mg	0.7 mg	0.8 mg
D.W.	25 mL	25 mL	25 mL	25 mL
Propylene glycol	7.5 mL	7.5 mL	7.5 mL	7.5 mL
Polyethylene glycol	7.5 mL	7.5 mL	7.5 mL	7.5 mL
Pioglitazone	50 mg	50 mg	50 mg	50 mg

Table 3: Results of each formula of thermos-adhesive gel.

Compositions	Formula					
	F1	F2	F3	F4	F5	F6
Poloxamer	2.5 g	2.75 g	3 g	3.25 g	3.5 g	3.75 g
Carbomer	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
D.W.	25 mL	25 mL	25 mL	25 mL	25 mL	25 mL
Result at 37°C to 39°C	Fluid	Fluid	Gel	Gel at 35°C and 36°C but at 37°C to 39°C it became mass	Mass	Mass

Table 4: Results of thermo-adhesive gel containing pioglitazone.

Compositions	Formula			
	F1	F2	F3	F4
Poloxamer	3 g	3g	3 g	3g
Carbomer	0.5 mg	0.6 mg	0.7 mg	0.8 mg
D.W.	25 mL	25 mL	25 mL	25 mL
Propylene glycol	7.5 mL	7.5 mL	7.5 mL	7.5 mL
Polyethylene glycol	7.5 mL	7.5 mL	7.5 mL	7.5 mL
Pioglitazone	50 mg	50 mg	50 mg	50 mg
Result at 37°C to 39°C	Fluid	Fluid	Fluid	Gel

Figure 9: The desired thermo-adhesive gel formula containing pioglitazone.

Table 5: Results of stability study of thermo-adhesive gel containing pioglitazone.

Parameters	Result of stability at (zero time) at ambient temperature	Result of stability at (40°C and 75% RH) after 1 month	Result of stability at (40°C and 75% RH) after 2 months
Color	No change	No change	No change
Oder	No change	No change	No change
Viscosity	Good	Good	Good
pH	5.7	5.8	6

However, limitations of this study include the absence of in vivo efficacy and comprehensive toxicity evaluation. Moreover, given the known systemic side effects of pioglitazone, future research should focus on optimizing targeted drug delivery systems that minimize systemic exposure while maximizing CNS targeting. Advanced carriers such as nanoparticles, liposomes, or ligand-conjugated gels could be explored to enhance the specificity and safety of intranasal formulations for neurodegenerative diseases.

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AUTHORS' CONTRIBUTION

Each author has made a substantial contribution to the present work in one or more areas, including conception, study design, conduct, data collection, analysis, and interpretation. All authors have given final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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