

Investigation of a Biodegradable Injectable *In Situ* Gelling Implantable System of Rivastigmine Tartrate

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Abstract

Introduction: Injectable *in situ* gelling solutions are novel implantable systems that combine the advantages of a prolonged release subdermal implant and the convenience of administration of an aqueous solution. **Objectives:** The aim of the present investigation was to formulate and evaluate a thermo-reversible injectable *in situ* gelling system of rivastigmine tartrate. **Methods:** Injectable *in situ* gelling solutions loaded with rivastigmine were formulated using the thermosensitive polymers: Pluronic F127 and Pluronic F68. The thermo-reversible gelling solutions were evaluated for gelation temperature, gel strength, syringeability and injectability, drug content, *in vitro* drug release studies, and *ex vivo* studies using extensor digitorum muscle of *Gallus gallus* domesticus. **Results:** Gelation temperature and gel strength increased with increasing concentrations of Pluronic F 68. All six formulations showed adequate ease on withdrawal and injection. The viscosity of formulations also increased with increase in the percentage of Pluronic F68 both in sol and gel form. An initial burst effect as a result of the immediate drug release from the sol form of the preparation before conversion to gel was observed from all formulations. Drug release was slower with an increase in the concentration of Pluronic F68. *Ex vivo* drug permeation studies for over 27 h exhibited slower release patterns from the selected formulations as compared to *in vitro* release. **Conclusion:** The developed formulations are capable of prolonging release of rivastigmine with the potential of achieving greater therapeutic success in Alzheimer patients compared to the conventional oral dosage forms.

Key words: Gelation temperature, *in situ* gels, implant, Pluronic F127, Pluronic F68, Rivastigmine tartrate

INTRODUCTION

Parenteral route is considered the most efficient for drug delivery in case of poorly bioavailable drugs. Rapid onset of action can be achieved even for the drug with narrow therapeutic window. However, in chronic diseases, repeated administration of drug is required to maintain systemic levels, and therefore, poor patient compliance would be expected as a result of the pain and discomfort involved.^[1] The formulation of repository injections that can control drug release and provide prolonged effects has taken care of many of the problems associated with frequent parenteral therapy. These long-acting injections control the release of drug for a week or month.^[2] However, these preparations have certain limitations such as administration problems due to high viscosity, clogging of needles, pain at the injection site, instability due to sedimentation, difficulties in maintaining

uniform particle size under aseptic conditions, homogeneity, and drug content uniformity.^[3] The use of subdermal implants has ensured better control over drug release with predictable release rates and is considered superior to repository injections in terms of efficacy and safety.^[2] However, many of these implants are solid devices which require surgical incision for placing the device in the subcutaneous tissue, and if non-biodegradable, may require retrieval after drug release is complete by surgical intervention.^[4]

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Recently, the concept of *in situ* gelling systems has generated a lot of interest in research and has been studied for diverse applications such as for nasal, ocular, oral, vaginal, and rectal routes. They are made up of biodegradable polymers such as gellan gum, alginate, pluronics, chitosan, or carbomers among many others. Solutions or dispersions of these polymers are converted to the gel state in the presence of certain environmental stimuli. The sol-to-gel transformation may be precipitated by a change in temperature, pH, ionic composition, or chemical reaction.^[5]

The potential of *in situ* gelling systems as injectable controlled release dosage forms has also been explored. When these formulations are injected into tissues or body fluids as solutions, are transformed into solid biodegradable implants at the site of injection. Thus, they combine the advantages of an injectable solution and that of a solid implant with respect to ease of manufacturing, dose accuracy, and injection, with the capability to control the release of the drug, thereby maintaining a defined blood level over a precise time period. Biodegradable injectable *in situ* gelling system can be considered as an alternative to microspheres, liposomes, suspensions, and emulsion as parenteral depot system. An important group of polymers for producing *in situ* gels are poloxamers or pluronics which are biodegradable, non-ionic triblock copolymers of ethylene oxide, and propylene oxide capable of forming thermo-reversible gels. Pluronic F68 and Pluronic F127 are widely used in drug delivery systems and are approved by the FDA for use as an “inactive” ingredient in oral solutions, suspensions, topicals, inhalations as well as in intravenous injectables.^[6] They form sols at room temperature and undergo sol-to-gel transition once injected into the body. In our investigations, we have used Pluronic F68 and Pluronic F127, the solutions of which gel at temperatures above 25°C.^[7] Moreover, the aqueous solutions of these polymers can be easily sterilized by filtration.

The drug selected for this study, rivastigmine tartrate (RT), is a reversible cholinesterase inhibitor indicated for the treatment of Alzheimer’s disease. It is available in the form of capsules and oral solutions (Exelon). Exelon capsules contain RT equivalent to 1.5 mg, 3 mg, 4.5 mg, and 6 mg, whereas Exelon oral solution contains RT equivalent to 2 mg/ml. The daily recommended oral dose in Alzheimer’s disease is 6–12 mg administered as a twice daily dose of 3–6 mg. The drug’s bioavailability is only 30% as it is extensively metabolized after oral administration.^[8]

Oral therapy of rivastigmine has many limitations that include poor absorption and bioavailability because of its hydrophilicity. The need for frequent dosing can give rise to cholinergic side effects such as gastralgia, nausea, cardiac arrhythmia, and loss of appetite.^[9] With respect to adhering to dosing schedule, there are chances of poor patient compliance since Alzheimer’s disease is associated with cognitive impairment and therefore inability of the patient to remember to take the dose at the right time. However, parenteral

administration requires the intervention of a skilled health professional if the formulation of rivastigmine was to be made in the injectable form which could avoid compliance issues. Therefore, the benefits of a prolonged release drug delivery are possible and problems related to frequent oral dosing, patient non-compliance, and drug toxicity can be avoided.^[10] So far, no work has been reported on the use of *in situ* gelling systems of the thermo-reversible type as injectable implants in the systemic delivery of RT. The objective of this study is to formulate RT-loaded *in situ* gelling solutions for injection use using thermos-reversible polymers, Pluronic F68 and F127 in various ratios, and investigate their feasibility for providing prolonged release of the drug after injection into a suitable tissue model.

MATERIALS AND METHODS

RT is a gift sample obtained from Cipla Ltd., Goa. Pluronic F 127 (PL127) or Poloxamer 407 and Pluronic F68 or Poloxamer 188 (PL68) were procured from Yarrow Chem Products, Mumbai. All other chemicals were of analytical grade.

Preparation of *in situ* thermo-reversible gelling solutions

The gel-forming solutions were prepared by cold method.^[11,12] Briefly, the polymers were dispersed in cold water at 4° in a beaker and stirred on a magnetic stirrer at 500 rpm for 2 h. The dispersions were diluted to the required volume with cold distilled water and then stored at 4° to obtain clear solutions. PL 127 and PL68 were used alone in concentrations of 10, 15, 20, and 25% w/v and in combinations of 20 or 25% PL127 with 1, 2, 3, 4, 5, 10, and 15% w/v of PL 68. The drug-free solutions were characterized for visual appearance, clarity, gelation temperature, gel strength, and rheological characteristics of syringeability and injectability. Based on the above characteristics, the optimized formulations were selected for drug incorporation. RT was incorporated as an aqueous solution such that the final concentration of the gelling solutions was 3 mg/2 ml. The solutions were adjusted to isotonicity with sodium chloride (9 mg/ml) and filtered through a 0.45 μ membrane filter before storage under refrigeration.

Evaluation of drug incorporated gelling solutions

Appearance and clarity

Visual appearance of the formulation with respect to clarity is an important parameter for the drug solutions that are parenterally administered. The presence of particulate matter not only affects patient compliance but also can be a source of tissue irritation or may even be harmful. All the formulations were inspected for clarity by visual inspection against black and white background under a strong light.^[13]

pH measurement

The pH was determined by bringing the electrode of the pen pH meter in contact with the surface of the formulations and allowing it to equilibrate for 1 min. The readings were taken as an average of three measurements.

Drug content determination

Drug content in the thermos-reversible gel was measured by UV-visible spectrophotometer. Each formulation (2 ml) was taken in a 10 ml volumetric flask and then diluted with phosphate buffer pH 7.4. The solution was then filtered and the absorbance was measured at 262 nm using an UV spectrometer. The test was conducted in triplicate and the average percentage drug content was determined.^[14]

Measurement of gelation temperature

The gel-forming solution was transferred to a small transparent beaker and was placed in a temperature adjusted thermostat controlled water bath that was maintained at 4°C. A magnetic bead was placed inside the beaker, and the solution was heated gradually with continuous stirring at 30 rpm. When the magnetic bar stopped moving due to gelation, the temperature displayed on the digital thermometer immersed in the solution was determined as gelation temperature.^[13]

Measurement of viscosity and gel strength

The viscosity of different formulation was measured using a Brookfield viscometer (Brookfield DV-II+ Pro) with T-bar spindle. The instrument was equipped with a temperature control unit, and the samples were equilibrated for 10 min before the measurement. The viscosity was measured at room temperature (28°C) and gelation temperature with the increase in angular velocity from 2 to 50 rpm.^[15,16] The average of three readings was considered for each measurement.

To determine the gel strength, the thermo-reversible gel-forming solution was put in a 100 ml graduated cylinder and gelled in a thermostatically controlled water bath at 37°C. A weight of about 50 g was placed on to the gelled solution. The gel strength was determined by noting the time in seconds required by 50 g of weight to penetrate 5 cm into the gel.^[17]

Syringeability and injectability

Syringeability and injectability of the formulations were evaluated on a qualitative basis. Syringeability was evaluated on the basis of the ease with which the formulation under test passed through the needle and injectability was evaluated on the basis of the ease with which the formulation was injected into isolated extensor digitorum (chick muscle).^[18] The extensor digitorum muscle from *Gallus gallus* domesticus was procured fresh from a reputable hatchery and the tissue weighing 4.5 g was excised. About 2 ml of formulation was drawn into a syringe with a 20 gauge needle and injected into

the muscle. To assess the syringeability and injectability, the following scores were given for both these parameters:

- +++Easily passed/injected
- ++Moderate
- +Difficult.

In vitro diffusion study

In vitro drug release study was carried out in a Franz diffusion cell using cellophane membrane as diffusion membrane. The cellophane membrane (previously soaked overnight in the buffer) was sandwiched between the donor and receptor compartment. A volume of 2 ml of the formulation was placed in the donor compartment. The receptor compartment was filled with 25 ml of phosphate buffer of pH 7.4 and was stirred continuously at 20 rpm. The whole assembly was placed on a magnetic stirrer, thermostatically controlled at 37.5°C ± 1°C to mimic physiological condition at which the formulation converts to gel form. At appropriate time intervals, aliquots (2 ml) were withdrawn and were replaced with equal volumes of fresh buffer to maintain sink conditions. The samples were filtered and absorbance was read at 262 nm using UV spectrophotometer-Jasco.^[19,20]

In situ gel formation in chick muscle

The extensor digitorum muscle from *G. gallus* domesticus was procured fresh from a reputable hatchery and the tissue weighing 4.5 g was excised. The formulation (2 ml) was injected into the muscle using a 20 gauge needle. Crystal violet dye was added previously to the formulation to increase the visibility of depot in the muscles. The tissue was tied to a tissue holder and immersed in the vessel of an organ bath containing 25 ml of phosphate buffer (pH 7.4) maintained at 37°C ± 2°C and aerated at constant rate of 10–12 bubbles/s. The formation of depot was determined by taking a section of muscle after injection of formulation and observing the presence of any gelled mass.

Ex vivo permeation of RT from in situ thermo-reversible gel

The extensor digitorum muscle from *G. gallus* domesticus as described earlier was used for studying the permeation profile of RT from selected formulations. The tissue weighing 4.5 g was excised and 2 ml of the formulation was injected using a 20 gauge needle. As described previously, the muscle was then quickly mounted in the organ bath containing 25 ml of phosphate buffer (pH 7.4). The buffer was maintained at 37°C ± 2°C and aerated at a constant rate of 10–12 bubbles/s. Samples of 2 ml of the release medium were withdrawn at predetermined time intervals and replaced with fresh buffer to maintain sink conditions.^[21,22] The samples were filtered and subjected to UV spectrophotometric analysis to determine the drug release profiles. The drug release study was carried out only for 8 h instead of 27 h as in the case of *in vitro* study due to the difficulty in maintaining the viability of the muscle tissue for that length of time.

RESULTS AND DISCUSSION

During the initial pre-formulation and optimization studies, it was determined that solutions prepared with PL 68 alone did not have any gelling characteristics while those with PL 127 alone showed poor gel strength or gelation temperatures that were too high ($>40^{\circ}$) or too low ($<35^{\circ}$). The optimum concentration of PL 127 was 20% w/v since higher concentrations did not increase the gelation temperature further. However, the addition of low concentrations of PL 68 (1–15% w/v) to 20% w/v PL 127 solutions produced gelation temperatures closer to 37° . This can be attributed to the fact that the thermo-gelling behavior of poloxamers arises out of the self-assembling of the molecules into micelles with a dehydrated polypropylene oxide (PPO) core surrounded by hydrated swollen polyethylene oxide (PEO) chains at the critical micellar concentration and temperature. At higher temperatures, micelles lose their water, become dehydrated, and form a gel. PPO being hydrophobic tends to raise the gelation temperature while hydrophilic PEO lowers it. PL 68 has a higher ratio of PEO to PPO as compared to PL 127. Therefore, small amounts of PL 68 added to PL 127 solutions can increase the proportion of PEO, which leads to a rise in gelation temperatures.^[23]

The drug-free polymer compositions were screened for visual appearance, clarity, gelation temperature, gel strength, syringeability, and injectability. Accordingly, six formulations were selected which showed satisfactory results after evaluation for the above parameters. The addition of RT did not in any way affect the clarity and transparency of the solutions. They were also free from visible particles and were mobile solutions when stored under refrigeration at 4° . The

composition of the final formulations prepared is given in Table 1.

pH measurement

The results for pH of formulations are given in Table 2. The pH of all the formulations was found to be in the range of 4.4–6.93. Since the normal volumes administered by subcutaneous injection do not exceed 1.5 or 2.0 ml, they are small enough to be diluted by tissue fluids and adjusted quickly to physiological pH of 7.4 so that possible pain or irritation due to pH will be transient. Moreover, a lack of buffer ensures rapid normalization of pH after injection.

Drug content determination

Results of drug content are summarized in Table 2. The drug content of the formulations was estimated and the results were in the range of 95–98%.

Measurement of gelation temperature

The data for determination of gelation temperature of thermo-reversible gel-forming solutions are given in Table 2. A gelation at temperatures of 35 – 37°C is considered optimum for development of thermosensitive *in situ* gelling formulation for the purpose of implantation since temperatures below 30°C would mean gelation at room temperatures and problems in manufacture, handling, and administration. On the other hand, gelation temperatures exceeding 37°C would result in the formulation remaining in the liquid state after administration.

The addition of PL 68 to PL 127 solutions increases the gelation temperature of the formulation nearer to the physiological

Table 1: Composition of thermo-reversible gel-forming solution of RS

Formulation code	Ingredients			
	PL 127 (% w/v)	PL 68 (%w/v)	RT (mg)	Distilled water up to (ml)
F1	20	2	30	20
F2	20	3	30	20
F3	20	4	30	20
F4	20	5	30	20
F5	20	10	30	20
F6	20	15	30	20

Table 2: Data for gelation temperature, gel strength, pH, and percentage drug content

Formulation code	Gelation temperature ($^{\circ}\text{C}$)*	Gel strength* (s)	pH*	Percentage drug content*
F1	34 ± 0.81	35 ± 2	6.19 ± 0.1	95.15 ± 0.35
F2	35 ± 0.02	35 ± 3	6.27 ± 0.03	95.48 ± 0.29
F3	36 ± 0.06	37 ± 2	6.81 ± 0.02	96.70 ± 0.33
F4	37 ± 0.03	38 ± 3	6.42 ± 0.06	96.05 ± 0.47
F5	37 ± 0.08	42 ± 5	6.93 ± 0.1	97.70 ± 0.34
F6	37 ± 0.22	45 ± 3	6.6 ± 0.08	95.15 ± 0.35

*Mean and SD of n determinations; $n=3$. SD: Standard deviation

range of temperatures. Gelation temperature exhibited a slight increase when the concentration of PL 68 was increased in the formulation. This increase as explained earlier is due to the thickening power of poloxamers in water and is related to the molecular weight and ethylene oxide/ propylene oxide ratio.^[23-25] Formulations F4, F5, and F6 gelled at or close to 37°C, indicating that they would be successful in the conversion from sol-to-gel form after subcutaneous injection. This evaluation therefore consolidates the influence of the relative concentrations of PL 68 and PL 127 on the gelation temperature.

Measurement of viscosity and gel strength

Viscosity is an important parameter that must be considered when designing *in situ* gelling solutions intended for subcutaneous injection both before and after thermoconversion. Attributes such as pain on injection, syringeability, and injectability of the formulations before thermoconversion are predominantly influenced by their rheology. Highly viscous formulations produce challenges during various process steps, such as transfer operations (pumping) and filtration, among others. After gelation at body temperature, it is important that the formulation has the viscosity necessary for localization in the tissue at the site of injection so as to provide prolonged diffusion of the drug molecules from the gelled matrix.

Single viscosity determinations of formulations at room temperature and gelation temperature at 20 rpm as presented in Table 3 show that the viscosity of all formulations demonstrated a sharp surge after thermoconversion, as the micelles become dehydrated and form gels. It was observed that the use of increasing strength of PL 68 resulted in a proportionate increase in viscosity from F1 (2%) to F6 (15%) both in sol and gel form. After thermoconversion, the increase in viscosity of gels with greater proportions of PL 68 was due to the formation of a denser polymeric network as a result of increased entanglement of the micelles of the two poloxamers.^[26]

It is important that gelling solutions as depot injections should have viscoelastic properties which directly impacts syringeability and injectability. Therefore, the rheological behavior of the formulations before and after thermoconversion was evaluated at increased shear stress by varying the angular velocities. The viscosity of the formulations was measured at room temperature with increase in angular velocity from 2 to 50 rpm. The drop in viscosity as the angular frequency increased from 2 to 50 rpm indicated that the solutions had shear thinning properties and therefore were pseudoplastic systems. Similar observations were made after thermoconversion of all the formulations; however, there appeared to be almost negligible differences in the shear thinning effects on viscosity between formulations. The rheological profile of the prepared *in situ* gelling systems of RT before and after gelation is shown in Figures 1 and 2.

Likewise, the gel strength was also found to be affected by concentrations of PL68. With the increase in the concentration of PL68, an increase in the gel strength was observed. The gel strength of the formulations was found in the range of 35–45 s. It would be expected that a greater gel strength would increase the resistance for diffusion of drug through the gel after administration and hence would produce a more prolonged drug release profile. The results are presented in Table 2.

Syringeability and injectability

Syringeability is the ability by which a formulation can be drawn and dispensed out of a syringe and injectability refers to the performance of the solution during injection and includes factors such as pressure or force required for injection.^[27] Both these attributes are influenced by the viscosity of the formulations before thermoconversion. Viscosity creates significant challenges in injectability since high viscosity requires high injection force that leads to increased pressure on injection inevitably causing pain. High viscous products can also deter the completeness of the injection (i.e., the percentage of dose delivered). Although F4 and F5 showed slight resistance to syringeability and injectability, nevertheless the remaining formulations could be easily

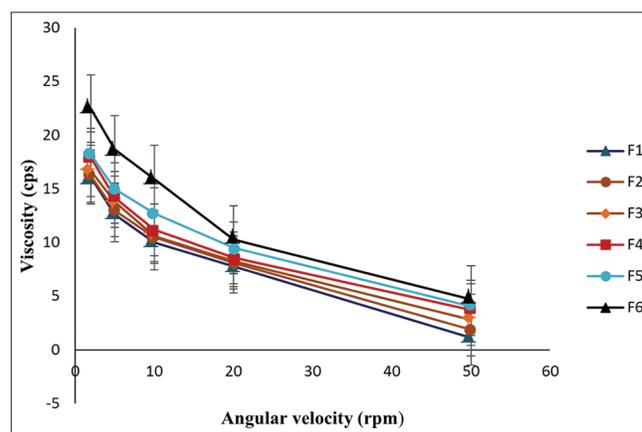


Figure 1: Comparative rheological properties of formulations before gelation

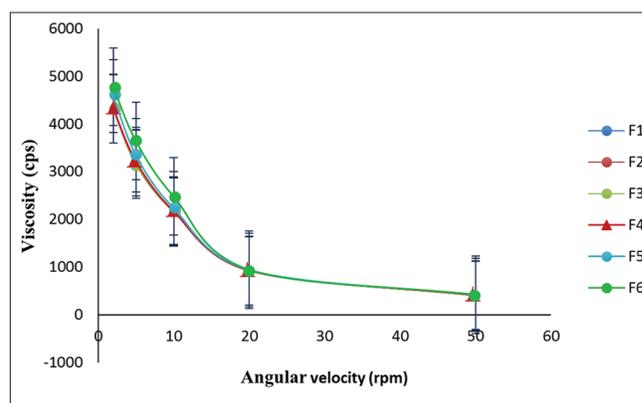


Figure 2: Comparative rheological properties of formulations after gelation

withdrawn into syringe and easily injected into the chick muscle, thereby reducing the potential to create problems during withdrawal of doses or produce pain on injection. It was demonstrated earlier that all the formulations had shear thinning properties and pseudoplastic in nature and therefore should not pose significant problems in syringeability or injectability as seen in the results given in Table 3.

***In vitro* diffusion study**

The release profiles of RT from the formulations in phosphate buffer of pH 7.4 using the Franz diffusion cell for 27 h are graphically represented in Figure 3. Significant drug release was not observed beyond 27 h from any of the formulations.

All the formulations showed an initial burst effect as a result of the immediate drug release from the sol form of the preparation before conversion to gel as seen in the initial phase of drug release profiles in Figure 3, after which the formulation undergoes thermoconversion to form a gel and results in sustained release of the drug. It was observed that the concentration of polymers affected the drug release from the formulations. There was a retardation of drug release with increase in the concentration of poloxamers. The formulations F2, F3, F4, F5, and F6 showed drug release beyond 24 h. The slowest drug release was observed for F6 which took 27 h to release a maximum of 99.58%.

The *in vitro* drug release data were subjected to kinetic analysis and fitted to zero-order and first-order models. The drug release mechanism was determined using the

Korsmeyer–Peppas equation, and the release exponent (n) was calculated by regression analysis.^[28]

The *in vitro* release profiles of the drug from all the formulations appeared to follow zero-order kinetics. This means that the formulations would provide drug release at a constant rate which is a desirable attribute of a controlled release dosage form.

The value of release exponent “ n ” obtained by applying Korsmeyer–Peppas equation for the formulations F1, F2, F3, F4, F5, and F6 was >0.5 and <1 as given in Table 4, and hence, the mechanism of drug release from these formulations followed anomalous or non-Fickian release, which could be attributed to the combination of diffusion and polymer surface erosion.

***In situ* gel formation in chick muscle**

The success of the designed formulations as *in situ* subdermal implants depends on their ability to form firm gels after the solutions are injected into the subcutaneous or muscle tissue, from where they should release the drug in a prolonged or controlled fashion. Therefore, this study was carried out to confirm the formation of a depot after injection of the solution into the excised chick muscle or extensor digitorum. To increase the visibility of the depot in the muscles, crystal violet dye was added to the formulation. The formation of depot was confirmed by taking a section of muscle after injecting the formulation. A semisolid violet-colored depot was observed in the muscle which confirmed the formation

Table 3: Data for syringeability, injectability, and viscosity of formulations

Formulation code	Syringeability	Injectability	Viscosity in cps at 20 rpm*	
			Before thermoconversion	After thermoconversion
F1	+++	+++	7.8±0.5	925.7±2.5
F2	+++	+++	8.1±0.2	926.1±1.2
F3	+++	+++	8.3±0.3	927.6±2.1
F4	+++	+++	8.6±0.4	930.9±0.7
F5	++	++	9.5±0.2	939.7±0.1
F6	++	++	10.3±0.2	946.7±1.5

*Mean and SD of n determinations; $n=3$. SD: Standard deviation

Table 4: Data for drug release kinetics of formulations

Formulations	Zero order	First Order	Korsmeyer–Peppas	Best fitting Model
	R^2	R^2	n	
F1	0.9243	0.9037	0.6741	Zero order
F2	0.9261	0.9430	0.6914	Zero order
F3	0.9550	0.9507	0.7244	Zero order
F4	0.9858	0.9107	0.7256	Zero order
F5	0.9913	0.8768	0.7805	Zero order
F6	0.9775	0.7445	0.7595	Zero order

of depot in the muscle. Depot formation in the muscle after thermoconversion of the *in situ* gelling solutions for the optimized formulations is shown in Figure 4.

An important attribute of subdermal implants is the ability to be retained in the subcutaneous tissue for a substantial period of time during which a sustained or a controlled release of drug is possible. This is conceivable since most implants are solid devices unlike injectable depot formulations which are liquids. Therefore, *in situ* gelling systems for implantation should be able to be retained in the subcutaneous tissue for as long as possible. Keeping this in mind, formulations that were optimized for the purpose of *ex vivo* drug release studies should be those that gel at body temperatures and provide greatest *in vitro* release for the longest period of time.

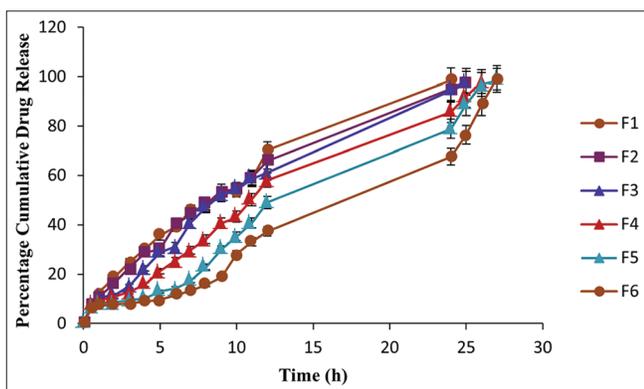


Figure 3: *In vitro* release of RS from formulations

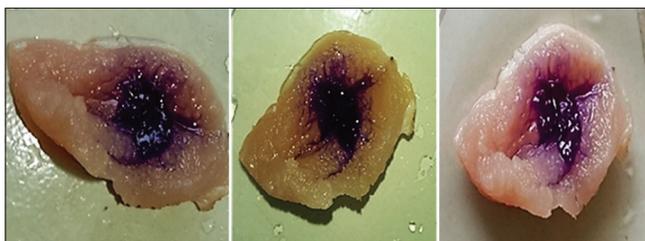


Figure 4: Formation of depot inside extensor digitorum muscle (a. Formulation F4, b. Formulation F5, c. Formulation F6)

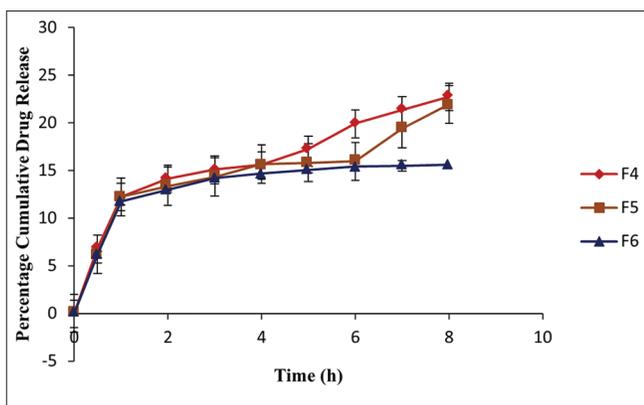


Figure 5: *Ex vivo* release profiles of RS from optimal formulations

Therefore, formulations F4, F5, and F6 were selected, and the drug release study was carried out only for 8 h instead of 27 h as in *in vitro* due to the difficulty in maintaining the viability of the muscle tissue for that length of time.

***Ex vivo* permeation of RT from *in situ* thermo-reversible gel**

The drug release of all three formulations as shown in Figure 5 was slow when compared to *in vitro* drug release due to the time required for the drug to diffuse through the muscle tissue before reaching the release medium in the organ bath. Unlike *in vitro* release, the initial burst effect was not so pronounced from the tissue probably for the same reason mentioned earlier. The lower viscosities of F4 and F5 provided lesser resistance to the diffusion of the drug through the gelled matrix and thereby enabled greater release. Formulation F6 showed an almost perfect constant drug release profile and the slowest. This is probably due to the fact that F6 has the highest concentration PL 68 which was responsible for highest viscosity and greatest gel strength, thereby providing the greatest resistance for the diffusion of the solubilized drug through the gel before reaching the release medium. Although the maximum percentage of drug permeated through the muscle was observed to be only 22% at the end of 8 h, nevertheless the results indicate that the three formulations showed promise of providing prolonged release beyond 27 h, if it was possible to conduct the *ex vivo* study for this period and beyond.

CONCLUSION

Formulation F6 could be considered as the best with good physical and gelling properties, slowest drug release profile *in vitro*, and an almost constant permeation profile *ex vivo*. Thus, this formulation can be used as an alternative to the conventional oral dosage forms of rivastigmine and could be a practical approach in the long-term management of Alzheimer's disease.

This work is only an attempt to explore the prospects of thermo-reversible gelling systems as tissue implants in the systemic delivery of drugs. There is much scope for improvement, such as the need for conducting tissue toxicity studies as well as evaluating pain and irritation potential of these formulations using a suitable animal model. However, the commercial production of such dosage forms could be cost-effective, besides having the advantages of the ease of scale-up and better reproducibility of manufacturing methods as compared to the more expensive solid implants.

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