An Injectable Sustained Release Lipid Based in situ Gel System of Aripiprazole for the Management of Schizophrenia

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ABSTRACT
Objectives: Development and evaluation of aripiprazole (AP) loaded lipid based in situ gel system (AP-LIGS) which could maintain the release of drug throughout period circumventing the need of oral therapy. Materials and Methods: AP possesses oral bioavailability (~87%) and biological half-life (~75 h) and undergoes extensive first-pass metabolism. Available AP long term injectable preparations have drawback of simultaneous administration of AP tablets orally for first few weeks, leading to patient non-compliance and making the therapy less effective. AP-LIGS was formulated using phospholipid E80, medium chain triglyceride and ethanol. Optimization was done by evaluating the effect of water content on viscosity of prepared AP-LIGS and % cumulative drug release (% CDR) at day 1. Results: Optimized AP-LIGS showed rapid gelation with minimum lag time and in vitro drug release profile up to 6 weeks. In vivo depot formation was confirmed by gamma scintigraphy after subcutaneous injection of liquid state of AP-LIGS. Histopathological study revealed its safety and biocompatibility with surrounding tissues since no alteration or any inflammation was observed at the injection site even after 45 days of subcutaneous administration. In vivo neurobehavioral assessment was done for assessing the efficacy of AP-LIGS system using Morris water Maze (MWM) test. MK-801 (Dizocilpine) model was used for inducing schizophrenia in Sprague-Dawley rats. All three parameters escape latency, time spent in target quadrant and total distance travelled was significantly improved (p <0.001) in AP-LIGS group when compared to MK-801 group at all time points. Conclusion: Developed novel AP-LIGS system is safe and may be used as a promising approach for sustained drug release and effectively manage schizophrenia. Key words: Aripiprazole, Gamma scintigraphy, Injectable, In-situ gel, Phospholipid E80, Schizophrenia.

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INTRODUCTION
Schizophrenia, a devastating and chronic psychotic disease is frequently associated with cycles of relapse and remission, due to its chronic nature it has a great impact on patient's ability to adapt socially.¹ According to the Indian Council of Medical research (ICMR) mental illness is rising at epidemic rates around the world, including India and WHO predicts that 20% of India’s population will suffer from some form of mental illness by year 2025.² Drugs used for the normal treatment of schizophrenia are generally classified as antipsychotics, neuroleptics and major tranquilizers.³ Antipsychotics drugs are first line of treatment which are further classified as typical or first generation antipsychotics (FGAs) examples loxapine, fluphenazine, perphenazine, haloperidol and loxapine whereas atypical or second generation antipsychotics (SGAs) are Clozapine, Olanzapine, Resperidone, Quantiapine, Palperidone, Ziprasidone etc.³ SGAs are hailed as a major advance, principally because of their lower liability for extra pyramidal side effects (EPS) and promised enhance efficacy and safety. SGAs claims superiority in terms of treatment of cognitive enhancement, negative symptoms and improved subjective tolerability and experience. These characteristics have led a general shift towards SGAs in the treatment of schizophrenia.³

Aripiprazole (AP) was given the U.S. Food and Drug Administration (FDA) approval on November 15, 2002 for the treatment of depressive, negative and positive symptoms which are related with schizophrenia. AP is a novel third generation atypical antipsychotic drug that is available as ABILIFY® Tablets, ABILIFY DISCMELT® Orally Disintegrating Tablets, ABILIFY® Oral Solution and ABILIFY® IM Injection.⁴ AP showed its effects through antagonism of 5-HT₂, alpha adrenergic receptors and agonism of 5-HT₁ and dopaminergic receptors.⁵ AP possesses oral bioavailability (~87%) and biological half-life (~75 h) and undergoes extensive first-pass metabolism.⁶ Injectable AP formulation has many advantages like higher bioavailability, avoidance of first-pass metabolism and sustained delivery of drug. Nevertheless, oral and intramuscular injection formulation of AP (for acute agitation) must be taken daily making the therapy less effective primarily due to non-adherence to long treatment cycles. Moreover, long acting IM formulation of AP due to the slow initial release requires oral supplementation for atleast 14 days making the therapy again less effective.⁷ Thus, the medical use of aripiprazole reduced markedly due to poor patient compliance resulting from repetitive injections. To overcome this problem sustained release drug delivery system provide several advantage over the normal formulation such as prolong drug delivery, decrease dosing frequency, reduced side effects and better patient compliance.⁸,⁹ In this study a novel injectable aripiprazole loaded in situ gel forming delivery system is developed using phospholipid E 80, medium chain triglycerides (MCT) and ethanol. Optimization was done by evaluating...
the effect of water content on viscosity of prepared LIGS and % cumulative drug release (% CDR) at day 1. The optimized formulation herein named as AP-LIGS system. Optimized AP-LIGS system was evaluated for \textit{in vitro} release behaviors. The safety of the optimized formulation was evaluated by histopathological studies. Gamma scintigraphy was performed for evaluating depot formation. For assessing the \textit{in vivo} pharmacodynamic efficacy, the optimized AP-LIGS system was administered s.c. in animals.

**MATERIALS AND METHODS**

**Materials**

AP (Drug) was received as gift sample from Sun Pharmaceutical Industries Ltd. (Gurugram, India). Phospholipid E 80 (Lipoid E 80) was purchased from Lipoid Co. Ltd (Ludwigshafen, Germany). Captex 355 and other Medium chain triglycerides (MCT) were generously obtained as gift samples from Abitec Corporation, USA and Gattefosse, USA respectively. MK-801 (Dizocilpine) was purchased from Sigma Aldrich, USA. Acetonitrile, ethyl acetate, methanol of HPLC grade and formic acid SQ grade were obtained from Merck (Mumbai, India). Milli Q HPLC water (Millipore, USA) was used for analysis. All other reagents were of analytical grade. The animal experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) of INMAS, DRDO.

**Methods**

**Preparation of Placebo Lipid Based \textit{in situ} Gel System (LIGS) and AP Loaded Lipid Based \textit{in situ} Gel System (AP-LIGS)**

The LIGS were prepared by first dissolving different quantities of phospholipid E 80 (P E80) in ethanol and then adding medium chain triglycerides at room temperature under constant stirring. For preparation of AP-LIGS, AP (100 mg) and P E80 was first dissolved in ethanol and then medium chain triglyceride was added into the mixture which was kept at room temperature under constant stirring.

**Screening of Excipients:** For screening, various \textit{in situ} gel systems were formulated by using three different medium chain triglycerides such as Captex 355, Labrafix\textsuperscript{TM} and Peceol\textsuperscript{TM} and varying the concentration of phospholipid E 80 (P E80) while keeping the concentration of ethanol (15%) constant throughout all the formulations. All preparations were evaluated on the basis of viscosity (<300 cP) of the resulting mixture. The composition of different excipients used for preparation of various \textit{in situ} gel systems was shown in Table 1. All experimentations were performed in triplicate.

**Viscosity Measurement of AP-LIGS**

Brookfield R/S plus rheometer (Brookfield Engineering Laboratories, Inc, Middleboro, USA) was used to measure the viscosity of AP-LIGS using a C50-1 spindle in triplicate mode. The torque value was maintained in the range 10-100% by setting rotating speed before starting viscosity measurement. During all experiments 37°C temperature was maintained.

**Optimization of AP-LIGS**

The effect of water content on the viscosity of prepared AP-LIGS and percentage cumulative drug release at first day (or day one) were deemed as optimization parameters for AP-LIGS.

**Effect of Water Content on the Viscosity of prepared AP-LIGS:** The prepared IGS having viscosity < 300 cP were further evaluated to find out the effect of adding different amount of PBS (0.01 M, pH 7.4) so that the final mixture had PBS content in the range of 0-48 % (w/w). Briefly, the developed LIGS were uniformly mixed with PBS by stirring for 10 min at 25°C and viscosity of the resultant uniform mixture was determined as stated below. The results were shown as the viscosity-PBS content curve.

**Percentage Cumulative Drug Release (%CDR) at day one:** The formulations selected after evaluation of viscosity-PBS curve were also assessed for the percentage of drug release at first day.

**In \textit{vitro} Drug Release Study**

To study \textit{in vitro} drug release, AP-LIGS (equivalent to 50mg AP), or AP suspension (50 mg) sample was introduced into dialysis bag (MWCO: 12,000 g/mol). This dialysis bag was put into a 200 ml glass beaker containing 100 ml of dissolution medium i.e. 0.1 N HCl (pH 1.2) having 1% Tween 20 at 37°C under stirring in a water bath. The release medium was exchanged to maintain the sink condition. At predetermined time schedule up to 45 days, release medium (0.5 mL) was taken and concentration of released drug was measured using previously published HPLC method with some modifications and re-validation.\textsuperscript{12} AP concentrations were determined using RP 18 (C\textsubscript{18}) Lichrospher\textsuperscript{100}, (250×4.6 mm) having particle size 5µm attached to an HPLC equipped with SCL 10A VP system controller (Shimadzu), quaternary LC-10 AT VP pump, SPD-10 AVP column oven (Shimadzu), variable wavelength programmable UV/VIS detector, Rhodyne injector fitted with a 20µL loop. The software used for the routine drug analysis was Class-VP 5.032. Chromatographic conditions used for separation were: temperature, 25 ± 2°C; flow rate, 1.0 mL/min; mobile phase, acetonitrile and 0.1 % formic acid in water (70:30 v/v); pH, 3.5; and detection wavelength of AP, 254 nm. All experiments were in triplicate.

**Histopathological Study of Skin**

The area around the site of injection of rats was shaved and rats were randomly divided into groups I and II (n=3). Samples (0.5 mL) of AP-LIGS and saline solution were injected subcutaneously to the group I and II respectively. At Day 0 and 45, the injection sites were visually examined and one rat from each group was sacrificed. The sections were stained with hematoxylin-eosin (H&E) and pathological analysis was done under the light microscope at 20 X magnification.

**Gamma Scintigraphy Study**

Radio labeling of AP-LIGS with \textsuperscript{99m}Tc: AP-LIGS formulation was radiolabeled with \textsuperscript{99m}Tc-pertechnetate as per optimized protocol SnCl\textsubscript{2} (stannous chloride) in dry form was used as a reducing agent. For labeling

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**Table 1: Different composition of excipients used for preparation of various \textit{in situ} gel systems.**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Medium Chain Triglycerides</th>
<th>Amount of Medium Chain Triglycerides (mg)</th>
<th>Amount of P E80 (mg)</th>
<th>Amount of Ethanol (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Labrafix\textsuperscript{TM}</td>
<td>100</td>
<td>750</td>
<td>150</td>
</tr>
<tr>
<td>F2</td>
<td>Labrafix\textsuperscript{TM}</td>
<td>200</td>
<td>650</td>
<td>150</td>
</tr>
<tr>
<td>F3</td>
<td>Labrafix\textsuperscript{TM}</td>
<td>300</td>
<td>550</td>
<td>150</td>
</tr>
<tr>
<td>F4</td>
<td>Labrafix\textsuperscript{TM}</td>
<td>100</td>
<td>750</td>
<td>150</td>
</tr>
<tr>
<td>F5</td>
<td>Captex 355</td>
<td>200</td>
<td>650</td>
<td>150</td>
</tr>
<tr>
<td>F6</td>
<td>Captex 355</td>
<td>300</td>
<td>550</td>
<td>150</td>
</tr>
<tr>
<td>F7</td>
<td>Captex 355</td>
<td>100</td>
<td>750</td>
<td>150</td>
</tr>
<tr>
<td>F8</td>
<td>Peceol\textsuperscript{TM}</td>
<td>200</td>
<td>650</td>
<td>150</td>
</tr>
<tr>
<td>F9</td>
<td>Peceol\textsuperscript{TM}</td>
<td>300</td>
<td>550</td>
<td>150</td>
</tr>
</tbody>
</table>
efficiency determination, ITLC (Instant thin layer chromatography) was performed.\textsuperscript{13}

**Gamma Scintigraphy Evaluation:** Depot formation of AP-LIGS formulation was confirmed by gamma scintigraphy method using male SD (Sprague Dawley) rats (approx. 250 g) (n=3). \textit{In situ} radiolabeled aripiprazole was administered \textit{s.c.} having 60 \textmu Ci of \textsuperscript{99m}Technetium pertechnetate in the back of the animal and at different time points i.e. 5 min, 6 and 12 hr images were taken using gamma camera (SPECT-CT Siemens T2, INMAS, DRDO).\textsuperscript{14} Throughout the study all the variables were kept constant.

**In vivo Efficacy Study**

**Morris Water Maze Test:** Spatial learning and memory in rodents was evaluated by Morris Water Maze test. This test is very common for evaluating neurobehavorial assessment in rodents.\textsuperscript{15} A dark shaded round water pool having measurements height 0.60 m and width 1.50 m was utilized as experimental set up. The circular pool was partitioned into four equal quadrants viz. NE, NW, SW and SE. The water was kept at 25 ± 2°C temperature in the pool throughout the experiment. During training sessions, at the focal point of target quadrant (NW), a square shaped platform was hidden and put 1 cm underneath the water surface. The rodents were trained for five consecutive days and four times in a day before continuing towards probe trial. The training was ended when the rodent found and got on to the platform or not able to find the platform by 2 min. The platform was removed and 24 hr after the last training probe task was conducted for the memory retention. Three parameters viz. time spent in target quadrant, the swim escape latency and path length was assessed by a video tracking software system (SMART v3.0.03, Panlab Harvard, U.S.).

**Experimental Design:** The rats were randomly divided into four groups' viz. group I to group IV containing six animals each (n=6). Total number of animals used was 24. To (a) control group: No MK-801 neither formulation was injected; (b) SZ group: MK-801 was given at day 0, 7 and 45, but formulation was not injected; (c) APS group: received subcutaneous AP suspension and MK-801 was given at day 0 and 7, (d) AP-LIGS group: received subcutaneous AP-LIGS formulation and MK-801 was given at day 0, 7 and 45. The probe task was performed at day 0, day 7 and day 45 and acquisition trial was conducted, before 24 hr of each probe task. On the probe trial day MK-801 and saline was administered \textit{i.p} and \textit{s.c.} respectively and all experimental variables throughout the study were kept constant.

**Statistical Analysis**

The $p < 0.05$ was considered to be significant. All the collected and quantified data were analyzed statistically using one-way and two-way ANOVA by Tukey’s test and Benforini test respectively. All the results were showed as mean ± standard deviation (SD).

**RESULTS**

**Preparation and Rheological Characterization of LIGS**

All the prepared formulations were clear transparent liquids of light yellow to dark yellow in color depending upon the concentration of P E80. As the concentration of P E80 increases the color of the prepared \textit{in situ} gel becomes darker. The viscosities of various LIGS prepared using Captex 355, Labrafac\textsuperscript{c} and Pecceol\textsuperscript{TM} were shown in Figure 1. The maximum and minimum viscosities were found to be with F7 and F6 i.e. 983.13 ± 2.04 and 13.37 ± 0.03 cP respectively. As reported earlier the threshold viscosity for an injectable liquid must be < 300 cP.\textsuperscript{16} All the prepared LIGS with Pecceol\textsuperscript{TM} were having viscosity more than permissible limit for injection which may be because of its higher viscosity of 220 cP at 25°C. So Pecceol\textsuperscript{TM} was found to be inappropriate for making \textit{in situ} gel systems. On the other hand viscosity of F1 and F4 was found to be 437.13 ± 0.52 and 395 ± 0.93 cP respectively which was also higher than the threshold range. This could be due to the high lipid content (75%) in both the LIGS as the concentration of lipid and medium chain triglycerides both play crucial roles in viscosity of final mixture of the system. Hence F2, F3, F5 and F6 having viscosities 145.9 ± 0.17, 16.27 ± 0.08, 120.87± 0.14 and 13.37 ± 0.03 respectively were selected for further evaluation.

**Optimization of AP-LIGS**

**Effect of Water Content on the Viscosity of Prepared LIGS:** For controlled drug delivery from \textit{in situ} gel system, the change in viscosity of the system from low initial viscosity before injection to high viscosity after injection is of supreme importance. For achieving this concentration of both phospholipid and medium chain triglyceride must be in optimum quantities. Thus the above selected LIGS systems i.e. F2, F3, F5 and F6 were further evaluated for their phase transition behavior with various PBS concentrations (% w/w) (pH 7.4, 0.01 M). The viscosity-PBS content curve is shown in Figure 2. As the PBS content increases the viscosities of all the LIGS also gets elevated up to a certain limit. The viscosity of F3 and F6 increased from 17.1 to 965.21 cP and 13.6 to 6428.5 cP respectively when PBS content rises from 4% to 36% (w/w). While in the same PBS content (% w/w) range F2 and F5 shows a significant increase in their viscosity i.e. 141.2 to 9356.1 cP and 112.6 to 823718.4 cP respectively. Thus, on comparing PBS-content curve of all the LIGS, F2 and F5 were found to be better candidates than F3 and F6 since they showed sharp increase in the viscosity initially which is...
useful in controlling the initial burst release of drug. On the other hand, F2 showed better viscosity-PBS content profile over F5 because of more rises in viscosity within the range. Moreover, it was also observed that after 36% PBS content there was decline in the viscosity-PBS content curve in all LIGS which could be explained due to the dilution effect of PBS. This viscosity change on addition of PBS solution is markedly contributed by the insolubility of phospholipid in aqueous solutions.17

Percentage Cumulative Drug Release (%CDR) at day one: The % cumulative drug release (%CDR) at day one from F2 and F5 were 11.64±2.8% and 23.7±4.1% respectively. F5 showed greater % CDR which might be due to more drug partitioning.18 Hence after considering both factors, F2 was selected as optimized formulation and Labrafac® as medium chain triglyceride for the preparation of optimized AP-LIGS.

**In vitro Drug Release Study**

The *in vitro* drug release studies for AP-LIGS were carry out by dialysis membrane method using dissolution medium 0.1 N HCl (pH 1.2) having 1% Tween 20 and AP suspension was used for comparison. The *in vitro* drug release profiles were shown in Figure 3. As expected, the percent cumulative release of AP from AP suspension was 62.75 ± 7.85 % and 87.48 ± 10.8 %, in 1 h and 2 h, respectively. On the other hand, AP-LIGS formulation showed sustained drug release for 45 days or more than 6 weeks with release of 9.73± 3.2%, 41.7± 6.8%, 68.41± 5.17%, 79.97± 4.72% and 89.39± 4.53% at 1 day, 7 day, 14 day, 30 day and 45 day respectively.

**Histological Study**

Histological studies were performed in rats to check any sign of irritation and histological aberrations by AP-LIGS system at the injection site since ethanol based delivery systems can cause skin irritation or inflammation. In saline group i.e. in group I no inflammation was observed at day 0 or even after 45 days of subcutaneous injection (Figure 4). While in group II i.e. treated with AP-LIGS system also there were no pathological alterations or ulceration were observed even after 45 days at the injection site or surrounding tissues.

**Gamma Scintigraphy Study**

Technetium has short half-life and due to which this study was done upto 12 hrs only and not continued further. The depot formation after subcutaneous injection of liquid AP-LIGS in rat was confirmed by *in vivo* scintigraphy (Figure 5). Gamma scintigraphic images were taken at 15 min, 6 hrs and 12 hrs time point. Figure 5A showed that within 15 min after s.c. injection of liquid AP-LIGS, depot formation occurs and throughout study duration it remained intact (Figure 5C). In Figure 5C spreading of radioactivity was observed, which indicates release of radiolabel-AP into the systemic circulation.

**In vivo Efficacy Study**

The effect of neurocognitive disorders on spatial learning was measured by Morris Water Maze (MWM) test in rodents. Time spent in target quadrant, escape latency and total distance travelled were the three parameters measured in MWM test. The results are shown in Table 2.

**Effect of AP-LIGS on Escape Latency in MWM test:** Administration of MK 801 significantly prolonged the escape latency (time to reach the hidden platform) in SZ group as compared to control group (*p* < 0.05). When animals were co-treated APS, there was no significant reduction in the duration of escape latency (*p* > 0.05) at day 7 and day 45 except at day 0 (*p* < 0.001), whereas co-treatment of optimized AP-LIGS system with MK 801 significantly reduced the duration of escape latency from day 0 to day 45 (*p* < 0.001).

**Effect of AP-LIGS on Time Spent in Target Quadrant in MWM test:** Administration of MK 801 significantly reduced the time spent in target quadrant in SZ group when compared to control group (*p* < 0.05) at all time points. When animals were co-treated with APS, there was significant increment (*p* > 0.01) on day 0 whereas showed insignificant increment on time spent in target quadrant on day 7 and day 45 (*p* > 0.05)
as compared to MK 801 treated group. Upon treatment of optimized AP-LIGS system with MK 801, significant increment (p < 0.001) in the duration of time spent in target quadrant was observed on day 0, 7 and 45 (P < 0.001) as compared to MK 801 treated group.

**Effect of AP-LIGS on Total Distance in MWM test:** Administration of MK 801 significantly increased the total distance travelled in MWM test as compared to control group (p < 0.05) on day 0, 7 and day 45. When animals were co-treated with APS, there was significant reduction (p > 0.001) on day 0 whereas showed insignificant reduction (p > 0.05) on the total distance travelled in MWM test as compared to MK 801 treated group on day 7 and day 45. Upon treatment of optimized AP-LIGS system with MK 801, significant reduction in the total distance travelled was observed on day 0, 7 and 45 (P < 0.001) as compared to MK 801 treated group.

**DISCUSSION**

In situ gel system is a sustained release system which is formulated with the help of polymers such as PLGA as well as with lipids such as phospholipid E 80, soya lecithin. Polymers are less compatible to the cells while phospholipid are one of the chief constituent of cell thus are more biologically compatible. Phospholipid exhibits poor aqueous solubility and hence on administration in liquid form, system may undergo phase separation and forms a solid or semisolid structure (in situ gels) at injection site. This could be because of exchange of water-ethanol between the surrounding body and the formulation. These are special type of formulation that is manufactured and administered in liquid forms and solidifies after administration and forms in-situ gel. Such in situ gel forming delivery systems (phospholipid based) have been applied for long term delivery of drugs such as bromotetrandine, doxorubicin and exenatide. In one of the previous studies it was reported that octreotide loaded in situ gel system showed in vivo release for 30 days.

Firstly, LIGS were formulated by simple mixing and stirring the various concentrations of PE80 and different MCT in ethanol for 30 min (Table 1). The LIGS formulated with three different MCT were evaluated based on initial viscosity (Figure 1) and four formulations viz. F2, F3, F5 and F6 with viscosity < 300 cP were selected for further evaluation. Optimization was done based on (a) viscosity change on addition of PBS (b) gel strength, (c) rapid gelation and (d) % CDR at 1 day. The viscosity-PBS content curve showed that formulations F2 and F5 showed sharp increase in viscosity compared to F3 and F6 (Figure 2). However, F2 showed highest gel strength and less burst release at day one in comparison to F5. Hence, F2 containing PE80: Labrafac® in ratio 65:20 was considered optimized and further evaluated.

Optimized AP-LIGS showed sustained drug release over a period of 6 weeks without burst effect (Figure 3). Sustained drug release could be due to combining effect of slow partitioning of lipophilic drug from AP-LIGS formulation to aqueous media, transition of phase of phospholipid to form gel and immiscibility of phospholipid in water. Histological studies showed no ulceration and inflammation at injection site even after 45 days of s.c. administration of AP-LIGS (Figure 4). These findings provided substantial evidence that all excipients and the amount of ethanol used in AP-LIGS system are relatively safe for living tissues. Hence, the developed system was found to be safe and biocompatible. In vivo gamma scintigraphy studies in rats showed depot formation occurs within 15 min following s.c. administration of AP-LIGS (Figure 5A), which remained stable upto 12 h (Figure 5C).

*In vivo* pharmacodynamic studies were performed in rats using MWM test for assessing the efficacy of AP-LIGS system. MK-801 in dose 0.5 mg/kg, i.p. was administered to developed AP-LIGS system which was tested using Morris Water Maze (MWM) test against MK-801 (Table 1). APS group showed protective effect from MK-801 on Day 0 and not beyond that which might be due to inability of AP suspension to release drug in a sustained manner for longer period. Whereas, AP-LIGS group showed protective effect from MK-801 upto 45 days which could be probably due to sustained release of drug from AP-LIGS formulation over period of 45 days as demonstrated by *in vitro* drug release. Hence, single subcutaneous injection of AP-LIGS showed protective efficacy against schizophrenia.

**CONCLUSION**

Parenteral controlled release lipid based *in situ* gel system of aripiprazole was formulated using phospholipid E80, medium chain triglycerides and ethanol. The *in vitro* drug release profile of AP-LIGS showed sustained drug release for upto 6 weeks with small initial burst (less than 10%). AP-LIGS converted into depot within 15 min of s.c. injection as revealed by gamma scintigraphic study and remained intact till other time points. Whereas, in histopathological studies no irritation and inflammation was observed at injection site which proved its biocompatibility and safety with surrounding tissues. The efficacy of the developed AP-LIGS system was tested using Morris Water Maze (MWM) test against MK-801 induced schizophrenia. All the three parameters in MWM test were found to be statistically significantly different (p < 0.001) from SZ (MK-801) group when evaluated at day 0, 7 and 45. Therefore, AP-LIGS may be useful as depot forming lipid based *in situ* gel system for improving patient compliance and managing schizophrenia.
ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AP: Aripiprazole; AP-LIGS: Aripiprazole loaded lipid based in-situ gel system; EPs: Extrapyramidal side effects; h: hour; HPLC: High performance liquid chromatography; i.p.: Intra peritoneal; LIGS: lipid based in-situ gel system; MCT: Medium chain triglyceride; MWM: Morris water maze test; P E80: Phospholipid E 80; s.c.: Subcutaneous; SD: Standard deviation.

REFERENCES