DEVLOPMENT OF NANOSIZED ARIPIPRAZOLE LOADED BIO-NANOGEL USING MENTHA ARVENSIS BIOPOLYMER AS A BIO-STABILIZER CUM BIO-RETARDANT

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ABSTRACT

The current research work aimed to formulate and evaluate Aripiprazole Bio-nanogel using Mentha arvensis as bio-retardant and bio-stabilizer for transcranial delivery. Aripiprazole is a partial dopamine agonist of the second generation (or atypical) class of antipsychotics that is primarily used in the treatment of schizophrenia, bipolar disorder, major depressive disorder (as an adjunct), and irritability associated with autism. The biopolymer from Mentha arvensis leaves was isolated by addition of optimized quantity of acetone non solvent & recovered by filtration & used as bio-retardant and bio-stabilizer & prepared Aripiprazole loaded bio-nanogel.[1] The bio-nanogels were prepared by nanoparticle dispersion in gel method using aripiprazole as model drug for trans-cranial delivery with Mentha arvensis (0.1%, 0.4%, 1%, 4%) using as bio-retardant and bio-stabilizer & with Pullulan (0.1%, 0.4%, 1%) using as standard polymer. The results were compared on mentioned parameters like pH, texture, spreadibility, % entrapment efficacy, preliminary determination of Nano size distribution by UV method & in-vitro drug release study. The experimental results revealed that the formulated Aripiprazole Bio-nanogels showed T50% of 12.9hrs and T80% of 20.7hrs respectively for FM2 (1:0.4) & T50% of 18.2hrs and T80% of 42.3hrs respectively for FP2 (1:0.4) were found to be the best formulation showing drug release profile in a controlled manner. The conclusion was drawn that Pudina (Mentha arvensis) used as biopolymer was safe and developed nanosized Aripiprazole loaded bio-nanogel will be more affective for brain targeting upon trans-cranial administration.

1. INTRODUCTION

Nanogels may be defined as Nano-sized hydrogel systems which are highly cross linked systems in nature involving polymer systems which are either co-polymerized or monomers. [2] Sudden outbreak in the field of nanotechnology have introduced the need for developing nanogel systems which proven their potential to deliver drugs in controlled, sustained and targetable manner. With the emerging field of polymer sciences it has now become inevitable to prepare smart Nano-systems which can prove effective for treatment as well as clinical trials progress. [3] Traditionally in the name of gels we have heard of semisolid formulations with three dimensional network of organic systems encompassing fluids and drugs. Prospects of targeted drug delivery perhaps could not been established with these preparations. [4] The significance of Nano-sized micro gel and hydrogel has arisen due to specific delivery system anticipation. Wide variety of polymer systems and the easy alteration of their physico-chemical characteristics has given advantage for versatile form of nanogel formulations. [5] Nanogels have revolutionized the field of gene therapy, since delivery of gene has now become possible within cellular organelles for gene silencing therapy systems. [6] Nanogels are typical formulations mainly of the size range of 100 nm, by varying solvent quality and branching the volume fraction can be altered variably to maintain a three dimensional structure. [7-8] The overall review suggests that innovation in this field shall bring forth sound support to cancer therapy in future.

The term Trans-cranial route means the brain targeted transfer of drug molecules across the cranium through the layers of the skin and skin appendages of the head, arteries and veins of the skin of the head, the cranial bones along with the dipole, the cranial bone sutures, and the meninges and specifically through the emissary veins. [9-10] The emissary veins draining blood from extra cranial sites into the intracranial sinuses pierce a series of foramina present in the cranial bones. Scalp veins communicate with the sinuses of the brain via emissary veins. There are thirteen emissary veins connecting extra cranial sites of the head with intracranial sinuses. [11] The unique anatomical arrangement of blood vessels and sinuses in the human skull and the brain, the prevalence of a high density of skin appendages in the scalp, extra cranial vessels of the scalp communicating with the brain via emissary veins and most
importantly, the way that the scalp is used in treating diseases associated with the brain show that a drug could be transcranially delivered and targeted to the brain through the scalp.\textsuperscript{[12]}

Aripiprazole is a partial dopamine agonist of the second generation (or atypical) class of antipsychotics that is primarily used in the treatment of schizophrenia, bipolar disorder, major depressive disorder (as an adjunct), and irritability associated with autism. Aripiprazole exhibits high affinity for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors, moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha1-adrenergic and histamine H1 receptors, and moderate affinity for the serotonin reuptake site. Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors. Atypical clinically help patients by transiently occupying D2 receptors and then rapidly dissociating to allow normal dopamine neurotransmission. This keeps prolactin levels normal, spares cognition, and obviates EPS. This, however, is not borne out by the results. While 5-HT2A receptors are readily blocked at low dosages of most atypical antipsychotic drugs (with the important exceptions of remoxipride and amisulpride, neither of which is available for use in Canada) the dosages at which this happens are below those needed to alleviate psychosis.\textsuperscript{[13]}

2. MATERIALS AND METHODS

2.1. Isolation of Biopolymer from \textit{Menthe arvensis}: 200g of \textit{Menthe arvensis} leaves were procured from the market. Then leaves were ground with 500 ml of distilled water in order to obtain the juice of the biomaterial in grinder. The biomaterial was soaked in 100ml of chloroform & kept for 1hrs for removal of oil. Then chloroform was removed through muslin cloth from the biomaterial. Then 500ml of distilled water was added in the biomaterial for soaking & kept for 24 hrs in refrigerator for settling of sediment. The supernatant of biomaterial was taken & centrifuged at 3000rpm for a period of 15 minutes. After centrifugation, the supernatant was taken & (half amount of biomaterial) 250ml of acetone was added after optimization & kept for 24hrs in refrigerator. Then biopolymer was separated from acetone & spread on the glass plate for air drying. After drying, the biopolymer was scrapped to the glass plate & the bio-material was passed through sieve #120 stored at room temperature. The bio-polymer extraction was repeated 6 times & practical yield was calculated.

2.2. Formulation of Aripiprazole bio-nanogel: The Aripiprazole nanoparticles prepared by addition of dextrose and dextran as a nanosizant and various proportion of bio-polymer \textit{Mentha arvensis} as bio-retardant (1:0.1, 1:0.4, 1:1 and 1:4) and Pullulan (0.1%, 0.4%,1%)
followed by optimized cycles of sonication. The nanoparticles were incorporated uniformly into the gel under magnetic stirrer mode which was prepared by sodium alginate (100mg), PVA (100mg) and HPMC (100mg) and prepared bio-nanogel was subjected. The drug was nanosized by using bath sonicator for 8 cycle(each cycle for 3 minute) similarly biomaterial Mentha arvensis in different ratio was nanosized which was dried in petri dish. 10 mg of drug was accurately weighed and varied ratio of Mentha arvensis biomaterial as biostabilizer and bioretardant was mixed together for each formulation with the addition of 10 ml of distilled water then it was subjected to sonication for 8 cycles. The above solution was poured into the glass pestle and after optimization, the gelling composition were added viz. sodium alginate(100mg),PVA (100mg) and HPMC (100mg). Then co-processing agents viz. 1000mg of urea,1ml of glycerin, and 1ml of propylene glycol were triturated properly in geometric progression with the above solution. Then the resulted solution was further subjected to magnetic stirring for 45 minutes. Bio-nanogels obtained and placed in well closed container & stored in refrigerator.

2.3. Evaluation of the formulated Aripiprazole loaded bio-nanogel: The formulated Aripiprazole loaded bio-nanogels were subjected for various evaluation parameters as pH, texture, spreadibility, %Entrapment efficacy, preliminary determination of Nano size distribution by UV method and in-vitro release study.

2.3.1. pH Measurement: The pH of formulated bio-nanogels was determined by pH meter. The pH meter was first of all calibrated using potassium chloride solution. Then after calibration the electrode is the first dipped in distilled water and then the pH of bio-nanogels were determined and the result were reported.

2.3.2. Texture: The texture of the formulated bio-nanogels was determined by applying the bio-nanogels on skin and the results were reported.

2.3.3. Spreadibility: 0.1ml of the bio-nanogels were taken and kept over glass plate. Then another glass plate was kept over it. The area covered by the bio-nanogels after 5 minutes were determined and the results were reported.

2.3.4. %Entrapment efficacy: The entrapment efficacy was determined in bio-nanogels, a weighed amount (10 mg) of Aripiprazole loaded bio-nanogels were suspended into 10 ml of distilled water. The resultant solution was filtered through 0.45mm what man filter paper.
This solution was assayed for drug content by U.V spectroscopy at \( \lambda_{\text{max}} \) 261nm & the corresponding absorbance was recorded.

**Entrapment efficacy was calculated according to the following formula**

\[
\text{Entrapment efficacy} = \left( \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \right) \times 100
\]

2.3.5. Preliminary determination of nanosize distribution by UV method

10mg of the bio-nanogels were dispersed in 10ml of distilled water. The resultant solutions were filtered through 0.45mm Whatman filter paper. These solutions were then subjected for determination of % transmittance at 200nm to 800nm respectively using shimadzu uv-vis spectrophotometer-1800. The % transmittance were determined and reported.

2.3.6. **In-vitro drug release:** In vitro drug release was performed by two methods

**Static method (M S Diffusion cell)**

**Dynamic method (Franz Diffusion cell)**

a) **M.S Diffusion Apparatus:** The In vitro drug diffusion was carried out in M.S diffusion apparatus. This was static method and employed complete replacement of the sample. 1ml of Aripiprazole loaded bionanogels was kept in the donor compartment and the receiver compartment was filled with 13 ml of buffer. The complete sample was withdrawn after 30 mins. And the receiver compartment was refilled with 13 ml of fresh buffer. The samples were withdrawn at regular time intervals for 12 hours. The amount of drug release was assessed by measuring the absorbance at 261nm using U.V spectrophotometer.

b) **Franz Diffusion Cell:** The Franz diffusion cell was used for studying the in vitro release. Dialysis membrane was tied to the terminal portion of the cylindrical donor compartment. 1ml Aripiprazole loaded was placed in donor compartment of Franz diffusion cell. The receptor compartment contained 7 ml of buffer solution of pH 7.4 maintained at 37°C under mid agitation using magnetic stirrer. At specific time intervals, sample of 3 ml were withdrawn and immediately restored with the same volume of fresh phosphate buffer. The amount of drug released was assessed by measuring the absorbance at 261 nm using U.V spectrophotometer.

2.3.7. **Stability studies:** Stability studies were conducted as per ICH Guidelines.

Stability testing of pharmaceutical product is done to ensure the efficacy, safety and quality of active drug substance and dosage forms and shelf life or expiration period. The stability
studies of the formulations were conducted at 40°C ± 2°C, 25± 2°C and 2 ± 5°C temperature values respectively. After every 15 days, the aggregation, nature, colour change, and in-vitro drug release of formulations was determined.

3. RESULTS AND DISCUSSION

3.1. Isolation of the biomaterial
The biopolymer was isolated from by simplified economic process. The optimization of biopolymer isolation process was repeated six times for and the % yield was calculated. During optimization the results obtained were reproducible with insignificant variation and can be adopted for scaling up in bulk manner. The % yield for biomaterial from leaves of *Mentha arvensis* was found to be of 2% w/w.

3.2. Physicochemical properties of the isolated biomaterial
The biomaterial obtained from leaves of *Mentha arvensis* was obtained in powdered texture that was dark green in color and odorless in nature, bitter in taste and solubility was reported in methanol and water. The biopolymer confirmed the presence of reducing sugar and absence of protein, starch and carbohydrates.

3.3. Drug excipient interaction studies: After performing the UV method shows λmax of drug-excipient mixture near about pure drug. So drug-excipient interaction study showed that there was no interaction between drug and biomaterial and biomaterial was compatible with the drug. As no any interaction was found, so it indicates that the bio-material was found useful in formulation bio-nanogels.(fig no.1)

3.4. Spectral studies of the isolated bio-materials
**IR Spectroscopy:** The result of IR spectra of biomaterial isolated from leaves of *Mentha arvensis* showed the peak 3126 cm-1, 2922 cm-1, 1400 cm-1, 1392 cm-1 and 500 cm-1 which clearly indicated functional groups RCO-OH, RCH2CH3CH, RCO-O- and R-Br respectively. (fig no.2).

3.5. Evaluation of formulated aripiprazole bio-nanogel

3.5.1. pH Measurement: The pH of the Aripiprazole loaded bio-nanogels prepared using biomaterial isolated from leaves of *Mentha arvensis* (FM1-FM4) were found in the range of 7.1 to 8.5. The pH of the Aripiprazole loaded bio-nanogels prepared using standard polymer Pullulan (FP1-FP3) were found in the range of 7.3 to 7.8. (fig no.3)
3.5.2. **Texture:** All the formulated Aripiprazole loaded Bio-nanogels [FM1-FM4, FP1-FP3] were found to have smooth texture on application on skin.

3.5.3. **Spreadibility:** The spreadibility of the Aripiprazole loaded bio-nanogels prepared using biomaterial isolated from leaves of *Mentha arvensis* (FM1-FM4) were found in the range of 3.5 to 5.5cm. The spreadibility of the Aripiprazole loaded bio-nanogels prepared using standard polymer *Pullulan* (FP1-FP3) were found in the range of 6.1 to 7.5cm. (fig no.4).

3.5.4 **%Entrapment efficacy**

The entrapment efficacy of the Aripiprazole loaded bio-nanogels prepared using biomaterial isolated from leaves of *Mentha arvensis* (FM1-FM4) were found in the range of 26%-86%. The entrapment efficacy of the Aripiprazole loaded bio-nanogels prepared using standard polymer *Pullulan* (FP1-FP3) were found in the range of 45%-76%. (fig no.5).

3.5.5. Preliminary determination of nanosize distribution by UV method

The preliminary size distribution of Bio-nanogels [FM1-FM4, FP1-FP3] were done by the determination of % transmittance using UV-VIS spectrophotometer (shimadzu-1800) which gave a preliminary idea about the size distribution of particles as smaller the particle more was the % transmittance and vice versa. (fig no.6 to 7).

3.5.6. **In-vitro drug release of aripiprazole loaded bio-nanogel**

In-vitro drug release of Aripiprazole loaded bio-nanogel using modified M.S diffusion cell: In-vitro permeation studies were performed for all the formulations. The mechanism of aripiprazole released from the bio-nanogels was studied by fitting the release data in different kinetic models such as Zero order, First order, Higuchi Matrix, Peppas Korsmeyer and Hixson Crowell and determining the $R^2$ values of the release profile corresponding to each model. Its % drug release, T50% and T80% were calculated and based on other parameters were arranged in decreased manner.

The drug release pattern for formulations FM1-FM4 containing biomaterial isolated from leaves of *Mentha arvensis* (pudina) based on the T50% and T80% was found to be FM2 (0.4%) > FM1 (0.1%) > FM3 (1%) > FM4 (4%). In-vitro drug release was performed for all the formulations and the data indicate that drug loaded formulations show the sustained release behavior. Graph was plotted between %CDR and time, the $R^2$ value, T50% and T80%
was calculated from graph, the FM2(0.4%) formulation was found to be the best formulation showing an $R^2$ value of 0.9952, T50% of 12.9hrs and T80% of 20.7hrs respectively. According to the release kinetics the best fit model was found to be Peppas Korsmeyer with Anomalous Transport as the mechanism of drug release.

The drug release pattern for formulations FP1-FP3 containing standard polymer Pullulan based on the T50% and T80% was found to be FP2 (0.4%) > FP1 (0.1%) > FP3 (1%). In-vitro drug release was performed for all the formulations and the data indicate that drug loaded formulations show the sustained release behavior. Graph was plotted between %CDR and time, the $R^2$ value, T50% and T80% was calculated from graph, the FP2(0.4%) formulation was found to be the best formulation showing an $R^2$ value of 0.9885, T50% of 18.2hrs and T80% of 42.3hrs respectively. According to the release kinetics the best fit model was found to be Peppas Korsmeyer with Anomalous Transport as the mechanism of drug release.

On comparing all the parameters, the formulation FM2(0.4%) of Mentha arvensis and FP2(0.4%) of Pullulan were found to be the best formulations as it showed better permeation and less T50% and T80% in less concentration of bio polymer among all the formulations.

The drug release pattern for the best formulations among all the formulations based on the T50% and T80% was found to be FP2 (0.4%)>FM2 (0.4%).

T50% and T80% are depicted in table to 3 to 6. The $R^2$ values, the best fit model, and the order of drug release of the formulations are depicted in Figures no.8 to 9.

3.5.7. Stability studies

The formulations were observed after every 7 days for 1 months and no significant change was observed in physical appearance (i.e.; color and odor) of the Aripiprazole loaded Bionanogels. All the formulations remained stable in all the storage conditions. Thus, this study confirmed that aripiprazole loaded bio-nanogel prepared were stable in different conditions.
Figure 1: Interaction studies of drug and biomaterial from *Mentha arvensis* by wet and dry method

![Figure 1](Image)

Figure 2: IR Spectra of *Mentha arvensis* biomaterial

![Figure 2](Image)

Table no.1-Formula of Aripiprazole loaded bio-nanogel using *Mentha arvensis*:

<table>
<thead>
<tr>
<th>Formula</th>
<th>FM1 (1:1)</th>
<th>FM2 (1:4)</th>
<th>FM3 (1:1)</th>
<th>FM4 (1:4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aripiprazole (mg)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2. Bioretardent/Bio-stabilizer: <em>Mentha arvensis</em> (mg)</td>
<td>10</td>
<td>40</td>
<td>100</td>
<td>400</td>
</tr>
<tr>
<td>3. Gelling composition: a). Sod. alginate</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>b). HPMC(mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>c). PVA(mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>4. Co-processing agent a). Glycerine(ml)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>b). Propylene glycol(ml)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>c). Urea(mg)</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>5. Distilled water(ml)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 2: Formula of Aripiprazole loaded bio-nanogel using *Pullulan* (Synthetic polymer)

<table>
<thead>
<tr>
<th>Formula</th>
<th>FP1 (1:1)</th>
<th>FP2 (1:0.4)</th>
<th>FP3 (1:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aripiprazole (mg)</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2. Bioretardent/Bio-stabilizer: <em>Pullulan</em> (Synthetic polymer) (mg)</td>
<td>10</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>3. Gelling composition: a). Sod. alginate</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>b). HPMC (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>c). PVA (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>4. Co-processing agent a). Glycerine (ml)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>b). Propylene glycol (ml)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>c). Urea (mg)</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>5. Distilled water (ml)</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Figure 3: Comparison graph of Ph Profile between Aripiprazole Bio-nanogel FM1 to FM4 and FP1 to FP3

Figure 4: Comparison graph of Spreadibility Profile between Aripiprazole Bio-nanogel FM1 to FM4 and FP1 to FP3
Figure 5: Comparison graph of % Entrapment Efficacy between Aripiprazole Bio-nanogel FM1 to FM4 and FP1 to FP3

Figure 6: Preliminary nanosize determination by UV method of Aripiprazole Bio-nanogel FM1 to FM4

Figure 7: Preliminary nanosize determination by UV method of Aripiprazole Bio-nanogel FP1 to FP3
Figure 8: In vitro Drug Release of Aripiprazole using *Mentha arvensis* by modified M.S Diffusion (FM 1 to FM 4)

Figure 9: In vitro Drug Release of Aripiprazole using *Pullulan* by modified M.S Diffusion (FP1 to FP3)

Table 3: T50% and T80% values of Aripiprazole bio-nanogel using *Mentha arvensis* Biopolymer

<table>
<thead>
<tr>
<th>Mentha arvensis Ratio</th>
<th>T50 % (hrs.)</th>
<th>T80 % (hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM1 (1:0.1)</td>
<td>12.9</td>
<td>20.7</td>
</tr>
<tr>
<td>FM2 (1:0.4)</td>
<td>6.9</td>
<td>16.1</td>
</tr>
<tr>
<td>FM3 (1:1)</td>
<td>6.6</td>
<td>15.3</td>
</tr>
<tr>
<td>FM4 (1:4)</td>
<td>6.6</td>
<td>15.3</td>
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Table 4: T50% and T80% values of Aripiprazole bio-nanogel using *Pullulan* synthetic polymer

<table>
<thead>
<tr>
<th>Pullulan Ratio</th>
<th>T50 % (hrs.)</th>
<th>T80 % (hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP1 (1:0.1)</td>
<td>14.3</td>
<td>33.3</td>
</tr>
<tr>
<td>FP2 (1:0.4)</td>
<td>18.2</td>
<td>42.3</td>
</tr>
<tr>
<td>FP3 (1:1)</td>
<td>12.7</td>
<td>29.5</td>
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</table>
Table 5: Kinetic Release of Aripiprazole Bio-nanogel using Mentha arvensis

<table>
<thead>
<tr>
<th>formulation</th>
<th>Zero order</th>
<th>1st order</th>
<th>Higuchi Matrix</th>
<th>Peppas</th>
<th>Hixson Crowell</th>
<th>Best fit model</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM1 (1:0.1)</td>
<td>0.9290</td>
<td>0.8935</td>
<td>0.9253</td>
<td>0.9850</td>
<td>0.9640</td>
<td>Peppas Korsmeyer</td>
<td>Anomalous Transport</td>
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<tr>
<td>FM2 (1:0.4)</td>
<td>0.9293</td>
<td>0.9612</td>
<td>0.9216</td>
<td>0.9952</td>
<td>0.9865</td>
<td>Peppas Korsmeyer</td>
<td>Anomalous Transport</td>
</tr>
<tr>
<td>FM3 (1:1)</td>
<td>0.8819</td>
<td>0.9803</td>
<td>0.9307</td>
<td>0.9875</td>
<td>0.9771</td>
<td>Peppas Korsmeyer</td>
<td>Anomalous Transport</td>
</tr>
<tr>
<td>FM4 (1:4)</td>
<td>0.9029</td>
<td>0.9763</td>
<td>0.9284</td>
<td>0.9868</td>
<td>0.9841</td>
<td>Peppas Korsmeyer</td>
<td>Anomalous Transport</td>
</tr>
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Table 6: Kinetic Release of Aripiprazole Bio-nanogel using Pullulan

<table>
<thead>
<tr>
<th>formulation</th>
<th>Zero order</th>
<th>1st order</th>
<th>Higuchi Matrix</th>
<th>Peppas</th>
<th>Hixson Crowell</th>
<th>Best fit model</th>
<th>Mechanism of action</th>
</tr>
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<tbody>
<tr>
<td>FP1 (1:0.1)</td>
<td>0.9069</td>
<td>.9724</td>
<td>.9347</td>
<td>.9857</td>
<td>.9545</td>
<td>Peppas Korsmeyer</td>
<td>Anomalous Transport</td>
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<tr>
<td>FP2 (1:0.4)</td>
<td>0.8982</td>
<td>.9610</td>
<td>.9175</td>
<td>.9885</td>
<td>.9442</td>
<td>Peppas Korsmeyer</td>
<td>Anomalous Transport</td>
</tr>
<tr>
<td>FP3(1:1)</td>
<td>0.8586</td>
<td>.9559</td>
<td>.9363</td>
<td>.9588</td>
<td>.9289</td>
<td>Peppas Korsmeyer</td>
<td>Anomalous Transport</td>
</tr>
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</table>

4. SUMMARY AND CONCLUSION

In this research work, the potential of nanosized aripiprazole loaded bio-nanogel for trans-cranial delivery is investigated. Bio-nanogels for trans-cranial use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water soluble, longer shelf-life, bio-friendly and pleasing appearance. These bio-nanogels are having major advantages on novel vesicular systems as well as on conventional systems in various aspects. Bio-nanogels are a relatively newer class of dosage form created by entrapment of large amount of aqueous or hydro-alcoholic liquid in a network of colloidal solid particles. Bio-nanogel formulations generally provide faster drug release compared with ointment and creams.

Biopolymer is used to prepare Bio-nanogels because of its biodegradability, biocompatibility, non-toxic, non-irritant in nature and no reaction on applying on the skin. Physicochemical Characterization of biopolymers such as colour, odour, taste, texture and chemical tests were carried out. These isolated biomaterials are rich in protein, fibres and carbohydrates. Biopolymer was found non-toxic in nature, so these are suitable for preparing bio-nanogels
for trans-cranial drug delivery. These biopolymers were devoid of irritancy to cranium surface because of its inertness, so these biopolymers were selected for formulating aripiprazole bio-nanogels.

Bio-nanogels were prepared by Nanoparticles dispersion in gel method which is the easiest and reproducible method to prepare bio-nanogels without need of any sophisticated instruments. Drug to Polymer ratio was chosen at four levels for leaves of *Mentha arvensis* FM1 (0.1%), FM2 (0.4%), FM3 (1%), FM4 (4%) and six levels of standard polymer Pullulan FP1 (0.1%), FP2 (0.4%), FP3 (1%).

Each formulated Aripiprazole loaded bio-nanogels were evaluated for various parameters such as pH which was found in the range of 7.0 to 8.5, texture which was found all formulations smooth in nature, spreadibility which was found in the range of 2.5cm to 7.8cm, % entrapment efficacy which was found in the range of 26% to 95%, preliminary determination of nanosize distribution and in-vitro drug release.

On the basis of evaluations parameters FM2 (0.4%) of *Mentha arvensis* and FP2 (0.4%) of Pullulan were selected as the best formulations.

Finally a smart conclusion was drawn out the isolated biopolymers showed its in-built ability to enhance the pharmalogical action, reducing the side effects and reduction of the dosing frequency of Aripiprazole. They can serve as a novel bio-retardant for the formulation of drug loaded sustained release nanoparticles for trans-cranial delivery through the layers of skin, meninges, trigeminal nerves, emissary veins, cranial bones and sutures. The isolated biopolymers were found to be safe, biodegradable, have good spreadibility and retardability. The researcher those working in this trans-cranial drug delivery can exploit further this route by formulating bio-nanogels, emulsions, multiple emulsions, Emulgel. The biopolymer also displayed its properties like formulation of drug loaded emulsion, drug loaded multiple emulsions, drug loaded bio-nanogel and drug loaded Emulgel along with biopolymer. The same was confirmed by suitably formulating and evaluation the drug loaded dosage form. Hence these biopolymer also served as bio-excipient by formulated various drug loaded dosage form. Constant progress is required in the understanding of principles and processes governing, so it was concluded that formulation of aripiprazole loaded bio-nanogel could be utilized as potential drug delivery system to brain specificity via trans-cranial delivery.
On the basis of all evaluated parameters, the best formulations showed promising significant, retardant, stability. Due to the presence of bio-retardant they need for the future study further preclinical studies including pharmacokinetics and pharmacodynamics properties of formulation in rabbit and clinical trial is required in healthy volunteers in order to commercialize for this concept of brain targeting via trans-cranial route and significant patient compliance.

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6. REFERENCES


13. Karnataka State Pharmacy Council, drug information and research Centre, 5 Dec 2013; 1-130.