ABSTRACT
Glimepiride is a Hypoglycemic agent or anti-diabetic drug administered orally, belongs to 3rd generation of Sulfonyl urea; it is widely used in the treatment of type 2 Diabetes Mellitus (DM) individually or with conjugation of other hypoglycemic agents. In preformulation study, Glimepiride shows poor and slightly pH dependent solubility and thus in order to increase its solubility inclusion complex of Glimepiride was prepared using β-Cyclodextrin (β-CD). The buccal films of Glimepiride β-CD complex equivalent to 6mg Glimepiride were developed by solvent casting method using different polymers, Carbopol 934, HPMC K4M and Eudragit L100. The formulations were prepared using 3² factorial design to explore the effect Carbopol 934 and HPMC K4M (as independent variable) on %drug release, swelling study (as dependent variable). FTIR and DSC data revealed that there is no interaction between Glimepiride and polymers. The films were evaluated for their thickness, uniformity content, folding endurance, weight uniformity, swelling index and surface pH. All the formulations exhibited satisfactory physicochemical characteristics. In vitro release was carried out in simulated saliva solution using modified USP type II apparatus at 50 rpm and optimization study was performed using design expert software. Ex vivo release studies were performed with optimized batch. Short-term accelerated stability study was carried out for three month and the formulation found stable for that period of time.

KEYWORDS: Glimepiride, inclusion complex, Carbopol 934, HPMCK4M, Buccal film, Mucoadhesion.

INTRODUCTION
Non–insulin dependent diabetes mellitus (NIDDM), also known as type 2 (formerly referred to as adult-onset diabetes mellitus); in which resistance to endogenous insulin action is developed by target tissues due to alterations in cell receptors and is characterized by progressive deterioration of normal pancreatic b-cell function. In the early stages of the disease, the b -cells of the pancreatic islets compensate for decreased insulin sensitivity by increasing insulin secretion. As the disease progresses, b-cell decomposition with impaired insulin secretion follows and sensitivity to insulin continues to decrease. Sulfonylureas directly stimulate insulin secretion. Glimepiride, an anti-diabetic drug, is a very potent medium-to-long acting third-generation
sulfonylurea. It stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites.

Among all sulphonyluresas, Glimepiride shows a minimal influence on risk of blockage of calcium channels in myocardial cells and data about the safety of use of Glimepiride in patients with coronary artery disease is available. Glimepiride appears to have a lower risk of hypoglycemia, compared to the other [4].

Therapeutic effectiveness of a drug depends upon the bioavailability and solubility of drug molecules. Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability. Though Glimepiride has 99% oral absorption, due to its high first pass metabolism it has a low and variable bioavailability while being the member of BCS class II it shows poor solubility. In the present study Glimepiride was selected as a drug candidate for the development of mucoadhesive buccal film because of its low molecular weight, short half life and lipophilicity. Poor aqueous solubility is caused by two main factors, first is strong intermolecular interactions which make the solubilization of the solid energetically costly and high lipophilicity [5].

**Cyclodextrin Complexation** [6]

1. **Stacking complexes** are driven by association of nonpolar area of drug and complexes agent this results in exclusion of the nonpolar area from contact with water.

2. **Inclusion complexes** are formed due to the ability of a compound to enclose in another complex. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes [6].

**Buccal Cavity as site for Mucoadhesive Drug Delivery System**

Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time [7]. The mucosa is relatively permeable with a rich blood supply. The buccal cavity has a very limited surface area of around 50 cm² but the easy access to the site makes it a preferred location for delivering active agents. Mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery [8]. Buccal film may be preferred over adhesive tablet in terms of flexibility and comfort. In addition they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. The process of mucoadhesion involving a polymeric drug delivery system is a complex one that includes processes such as wetting, adsorption, diffusion, electronic, interpenetration of
polymer chains and fracture theories\cite{9,10}. To penetrate the mucosa to a significant degree, a drug should have relatively low molecular weight and should exhibit biphasic solubility patterns i.e. the drug should be soluble in the aqueous salivary fluid and shows penetration through lipid membrane. Glimepiride shows practically insolubility in aqueous fluid. Hence in the present study, inclusion complexes of Glimepiride were prepared. And films were prepared using Carbopol 934 and Hydroxypropyl methyl cellulose (HPMC K4M) as film-forming and mucoadhesive polymers by solvent casting method and molded into glass plates fabricated, consisting total area of 64 cm$^2$. Glimepiride shows the high protein binding capacity and influence of food on absorption in conventional tablet dosage form, which can be terminated by buccal dosage form. Thus use of Glimepiride mucoadhesive films for type 2 diabetes would be beneficial to get sustain release and to enhance bioavailability.

MATERIAL AND METHODS:

Materials: We received Glimepiride and Carbopol 934 as a gift sample from Glenmark Pharmaceuticals Pvt. Ltd., Nashik. HPMC K4M and β-CD were purchased from Thomes bakers (chemicals), Mumbai. All other chemicals used were of analytical grade and were used without further purification.

Methods:

1) Preparation of β-CD complex of Glimepiride:
β-CD complex of Glimepiride of different molar ratios (1:0.5, 1:1, 1:2) were prepared by Kneading Method. For this accurately weighed β-CD in first taken into mortar and its slurry is formed using 50% Ethanol while slow triturating it. To this slurry so formed previously weighed drug i.e. Glimepiride was added in parts with continuous trituration to ensure uniform distribution. The trituration was continued for an hour. The complex so obtained is then air dried, passed through sieve of mesh size 80 and used for further evaluation.

1. XRD of β-CD complex of Glimepiride\cite{6}:
X-ray powder diffraction patterns were obtained for the samples of pure Glimepiride and its inclusion complex with β-CD (1:2) using a Rigaku Miniflex X-ray diffractometer fitted with a scintillation counter and divergent beam monochromator with a radiation source. Data were collected between 5°C to 50°C on 2θ with a collection time of one second per step.

2. FTIR Study \cite{6}
The dry sample of the 1:2 Glimepiride-β CD complex was mixed with IR grade KBr in the ratio of 1:10 Sample preparation involved mixing the sample (2 mg) with potassium bromide (KBr),
triturating in glass mortar and finally placing in the sample holder. The spectrum was scanned over a frequency range 4000-400 cm\(^{-1}\) using Shimadzu, 8400S FTIR instrument.

**3. Dissolution study** \(^7\)

Dissolution study of the prepared inclusion complexes (1:0.5, 1:1, 1:2) and pure drug was carried out using Electrolab Dissolution apparatus (USP type-2). Phosphate buffer of pH 6.8 was used as dissolution media and dissolution was carried for 1 hour. Sampling was done at the time intervals of 15, 30, 45 and 60 min. Further concentration of the dissolved drug was determined by UV visible spectrophotometry analysis.

**II) Preparation of Buccal film of Glimepiride:**

The films of the Glimepiride β-CD complex (1:2) were prepared by solvent casting method\(^{11}\).

For the preparation, weighed amount of Carbopol 934, HPMC K4M dissolved in sufficient quantity of distilled water allowed to form viscous, homogenous polymeric solution and stirrer with glass rod. Accurately weighed and previously prepared Eudragit gel in Ethanol was added to above polymeric mixture. Previously prepared and weighed quantity of Glimepiride was dissolved in above polymer solution with continuous stirring on magnetic stirrer for 30-40 min.

At last calculated amount of Propylene glycol, Mannitol and Menthol dissolved in little water also added this drug polymeric solution. This solution was mixed thoroughly to obtain homogeneous solution and stirring on magnetic stirrer for 30-45 min and is kept undisturbed overnight for escalation of air if entrapped. The homogeneous solution was then put in to the glass mould having an area of 64 cm\(^2\) and dried at room temperature for 48 hrs.

**Table 1: Compositions of formulations using factorial design**

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride Complex with β-CD</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>25</td>
<td>25</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Eudragit L100</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Propylene Glycol (ml)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mannitol</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ethanol+Water (ml)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
II) Optimization by $3^2$ Factorial Designs:
The $3^2$ full factorial design was adopted for formulation design purpose. A $3^2$ full factorial design was adopted and the amount of polymers, Carbopol 934 (X1) and HPMC K4M (X2) were taken as independent variables. The factors were studied at three levels ($-1$, 0, $+1$) indicating low, medium and high, respectively, as represented in Table. The statistical optimization procedure was performed with the help of optimization software Design Expert 9.0.3.1. The software performs analysis of variance (ANOVA) and statistical optimization.

Independent variables

1) Concentration of Carbopol 934 ($X_1$)

2) Concentration of HPMC K4M ($X_2$)

Response variables (Dependent variable)

1) % Drug Release ($Y_1$)

2) Swelling index ($Y_2$)

Table 2: $3^2$ factorial design

<table>
<thead>
<tr>
<th>Factor level</th>
<th>Coded Form</th>
<th>Carbopol 934</th>
<th>HPMC K4M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>-1</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Medium</td>
<td>0</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>High</td>
<td>+1</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

EVALUATION PARAMETER FOR THE BUCCAL FILM OF GLIMEPIRIDE$^{[12, 13, 14]}$:

1. Thickness: The prepared film was divided into 2 X 2cm (4 cm²) and the thickness was measured at different strategic locations like four corners and center of each film. Mean SD was calculated. Using micrometer screw gauge and the average thickness was reported.

2. Weight uniformity: Weight variation was studied by individually weighing 10 randomly selected film strips and calculating the average weight by digital weighing balance.

3. Surface pH: Surface pH of film was determined to check whether the film causes irritation to the mucosa. The surface pH study was carried out by selecting 3 films randomly.

4. Morphology Study: The morphology of the films was studied for their appearance, texture and clarity.

5. Swelling index (SI):

Buccal films were weighed individually (designated as $W_1$) and placed separately in 2% agar gel plates, incubated at $37^\circ C \pm 1^\circ C$, and examined for any physical changes. At regular 1-hour time...
intervals until 4 hours, patches were removed from the gel plates and excess surface water was removed carefully using the filter paper. The swollen patches were then reweighed (W2) and the swelling index (SI) was calculated using the following formula:

\[ SI = \frac{W_2 - W_1}{W_1} \times 10^0 \]

Where; SI → Swelling index, W2 → final weight, W1 → initial weight

The experiments were performed in triplicate, and average values were reported.

6. **Folding endurance:**

Number of times a film can be folded at the same place without breaking or cracking gives the value of folding endurance. This was determined by repeatedly folding the films at the same place until it broke.

7. **Mucoadhesive strength:**

Mucoadhesion was evaluated using a texture analyzer (TexturePro CT V1.4 Build 17); setup for adhesion experiments controlled by the Texture Exponent software with 50 N load cell equipped with mucoadhesive holder. Experimental conditions, such as the contact force, contact time and probe speed, were selected based on preliminary experiments. A film was carefully attached to a 10-mm cylindrical probe (TA probe) by a double-face tape and then the polymer sample was brought toward the mucosa at a constant speed of 0.5mm/s, until a predetermined compressive force of 1 N was applied for 60s. The probe was then removed at 0.5mm/s to a distance of 15 mm and maximum detachment force (N) was determined for each sample.

8. **Drug content uniformity:**

Three films were randomly selected from the prepared ones were checked for dimensions and weight. Sample film of 4cm² was cut into small pieces and transferred to 100 ml volumetric flask. 100 ml of phosphate buffer pH 6.8 was added in the volumetric flask and this solution was sonicated for 30 minutes and the volume was made up to the mark using same solvent, filtered and the absorbance of the solution was recorded at 228 nm by UV Spectroscopy.

9. **In vitro dissolution:**

The in vitro dissolution study was carried out using USP type II (Paddle apparatus). The dissolution medium comprised 500 ml of phosphate buffer pH 6.8 maintained at a temperature of 37±0.5°C and paddle rotation speed of 50 rpm was used. One side of the buccal film was attached to a glass disk with instant adhesive. The disk was put in the bottom of the dissolution vessel so that the film remained on the upper side of the disk. Samples (5 mL) were withdrawn at pre-determined time intervals and replaced with fresh medium. The samples were filtered
through 0.45mm whatman filter paper with appropriate dilutions with phosphate buffer pH 6.8 and were assayed by UV-Visible spectrophotometer at 228nm.

10. Accelerated Stability Study:
Films of optimized batch were selected for stability studies. For these formulation were wrapped with aluminum foil and stability study was carried out for its physical characteristics at the predetermined one month intervals of 1st month, 2nd month and 3rd month like appearance (color changes), pH, swelling index and % drug release.

**Table 3: Test conditions for stability study**[15, 16]

<table>
<thead>
<tr>
<th>Test Conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of study</td>
<td>3 months</td>
</tr>
<tr>
<td>Temperature conditions</td>
<td>40± 2°C</td>
</tr>
<tr>
<td>Relative humidity conditions</td>
<td>75± 5%</td>
</tr>
<tr>
<td>Frequency of testing the samples</td>
<td>1st month, 2nd month, 3rd month</td>
</tr>
</tbody>
</table>

RESULT AND DISCUSSION
The preformulation studies such as determination of solubility, determination of melting point were performed and compatibility of drug and excipients were assured by FTIR and DSC studies. In the present study different formulations with variable concentration of polymers were prepared and evaluated for physico-chemical parameters; *in vitro* release and stability study and other evaluation parameter of mucoadhesive buccal film.

1) FTIR study:
The absorption band shown by Glimepiride is characteristic of the groups present in their respective molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Glimepiride and the absence of any well-defined unaccountable peaks is a confirmation of the purity of the drug sample[17].
Figure 1: FTIR study of a) Glimepiride, b) Drug and Polymer mixture, c) Drug and β-CD complex
II) Evaluation of β-CD complex of Glimepride:

a) XRD study:

From the above fig. 2, XRD of Glimepride shows high intensity sharp peaks at 14° & 21° C. Inclusion complex shows disappearance of important spectral lines and appearance of new peaks corresponding to new solid crystalline state. In XRD study of Glimepride inclusion complex peaks appear to be broadened, blunt and peak intensity of complex are diminished w.r.t. pure Glimepride due to rapid precipitation of the complex during preparation that ensure change in crystallinity.

b) FTIR study:

The FTIR study of drug complexed with β-CD is performed using Shimazdu 8400S FTIR system equipped with a computerized data station. As shown in figure 1, the FTIR Spectra of Glimepride-β CD Complex shows N-H stretching at 3371.68 cm\(^{-1}\), C-H stretching at 2931.9 cm\(^{-1}\), C=O bending at 1137.31 and N=O stretching at 1350-1550 cm\(^{-1}\); thus it is concluded that changes in peaks as compare to that of pure drug occurred due to complexation and it ensures the formation of the complex.

c) Dissolution Study
Dissolution study of the pure drug Glimepiride and inclusion complex of Glimepiride of varying ratios (1:0.5, 1:1, 1:2) was carried using USP type 2 apparatus. There observed a 1.75 fold increased rise in dissolution of 1:2 Glimepiride complex as that of pure drug.

Figure 3: Dissolution study of the inclusion complex of Glimepiride

III) Evaluation of Buccal film of Glimepiride:

Table 3: Physico-chemical characterization of Glimepiride buccal films

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Thickness of Film</th>
<th>Weight variation of film</th>
<th>Uniformity of content</th>
<th>Folding endurance</th>
<th>Mucoadhesive strength (dyne/cm²)</th>
<th>Swelling Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.026±0.02</td>
<td>52.9±2.84</td>
<td>96.99 ± 0.96</td>
<td>298±1.2</td>
<td>4.94 ± 1.05</td>
<td>68.5±3.28</td>
</tr>
<tr>
<td>F2</td>
<td>0.03±0.01</td>
<td>48.1±3.02</td>
<td>96.64 ± 1.10</td>
<td>320±1.09</td>
<td>5.29 ± 1.44</td>
<td>69.0±1.07</td>
</tr>
<tr>
<td>F3</td>
<td>0.03±0.06</td>
<td>50.8±2.82</td>
<td>96.11 ± 2.32</td>
<td>287±1.61</td>
<td>5.87 ± 1.07</td>
<td>69.3±3.21</td>
</tr>
<tr>
<td>F4</td>
<td>0.033±0.05</td>
<td>44.01±2.4</td>
<td>97.39 ± 2.89</td>
<td>309±1.42</td>
<td>7.06 ± 1.1</td>
<td>73.9±2.44</td>
</tr>
<tr>
<td>F5</td>
<td>0.033±0.05</td>
<td>51.8±2.39</td>
<td>97.65 ± 1.37</td>
<td>312±1.14</td>
<td>7.49 ± 1.34</td>
<td>74.0±1.3</td>
</tr>
<tr>
<td>F6</td>
<td>0.036±0.04</td>
<td>49.7±2.00</td>
<td>98.49 ± 1.12</td>
<td>324±1.51</td>
<td>8.54 ± 1.51</td>
<td>75.4±2.96</td>
</tr>
<tr>
<td>F7</td>
<td>0.04±0.06</td>
<td>48.9±2.23</td>
<td>96.59 ± 0.65</td>
<td>320±1.02</td>
<td>8.97 ± 1.59</td>
<td>79.4±3.14</td>
</tr>
<tr>
<td>F8</td>
<td>0.046±0.05</td>
<td>50.8±2.48</td>
<td>96.43 ± 2.42</td>
<td>329±1.08</td>
<td>9.07 ± 1.31</td>
<td>78.8±1.45</td>
</tr>
<tr>
<td>F9</td>
<td>0.05±0.01</td>
<td>52.3±1.88</td>
<td>97.80 ± 1.51</td>
<td>332±1.26</td>
<td>9.36 ± 1.36</td>
<td>80.2±2.54</td>
</tr>
</tbody>
</table>
All the prepared formulation shows satisfactory organoleptic properties. Drug content of all developed batches was found within limits i.e. 96.11% to 98.49%. Folding endurance of all the batches reflex good flexibility, batch F6 shows folding endurance of 324±1.51. Swelling behavior of the various batches gives satisfactory results. It is found to be influenced by concentrations of hydrophilic polymers Carbopol 934 and HPMC K4M. Mucoadhesive strength test of the formulation batches showed satisfactory results with optimum mucoadhesive strength of batch F6. From the results obtained parameters were observed to be influenced directly by amount of mucoadhesive polymer. From the results obtained, swelling index of the different formulation batch was influenced by the concentration of hydrophilic polymer i.e. Carbopol 934 and HPMC K4M. With increased amount of hydrophilic polymers the water/moisture uptake capacity of the formulation increases. The mucoadhesion also increases with the increased degree of hydration till the point of distanglement at the polymer- tissue surface that leads to abrupt drop in mucoadhesive strength due to overhydration. While appearance and strength of the films are influenced by Eudragit L100. Other evaluation parameters such as thickness, weight uniformity gives satisfactory results. Surface pH of all batches was also observed compatible to that of buccal saliva.

» In-vitro Drug release:

![Figure 4: Comparative In-Vitro Drug Release Profile of F1-F9 Formulations](image)

From the dissolution profile as shown above batch F6 give 98.12% release for 6 hrs. From the obtained results; Carbopol 934 which gets ionized state at salivary pH, polymeric network get
loosened attributing for higher drug release while increase in swelling increases the barrier effect for the drug release.

**IV) Optimization study:**

![Figure 5: 3-Dimensional plot for independent variable a) Drug release & b) Swelling index](image)

The 3D response surface plot factorial model was drawn to show the effect of the variables on %Drug Release (a) and Swelling index (b). The above figure (a) illustrates the effect of Carbopol and HPMC on the %DR. It can be concluded when the conc. of Carbopol and HPMC increases, the % Drug Release also gradually increases up to the conc. 25mg and 10mg respectively of Carbopol and HPMC and thereonwards, it decreases with the increase in polymer concentration. It can be seen that carbopol concentration majorly affects drug release than HPMC. And the figure (b) illustrates the effect of Carbopol and HPMC on the Swelling index. It can be concluded when the conc. of Carbopol and HPMC increases, the Swelling index also increase, it means swelling index has linear relationship with Carbopol 934 and HPMC K4M concentration.

**V) Stability Study Analysis:**

Stability study of the optimized batch F6 is carried out for the period of three months and various physical and chemical tests carried out; at the test intervals of 1, 2 and 3 months. There was no
significant change in appearance, surface pH and swelling index of the formulations as compared to that of zero day formulation.

**Dissolution Study of optimized batch F6 for stability studies:**

![Graph showing dissolution profile of optimized batch F6 for stability studies](image)

**Figure 6: Dissolution profile of optimized batch F6 for stability studies**

Stability study indicates that dissolution of optimized F6 batch gives no visible changes in the appearance of the film at each month interval till the end of the storage period as (as given in table). There was a little change in all but it’s negligible. Still drug release of the film at each month interval does not match as compared to the optimized batch but shows very little difference. As there was negligible change & no change in physical appearance it indicates that the development formulation was stable.

**CONCLUSION**

Glimepiride mucoadhesive films could be satisfactory to ensure optimum Glimepiride levels for prolonged duration of time (360 minutes). Buccal films of Glimepiride were successfully prepared using Carbopol 934, HPMC K4M and Eudragit L100 as polymers and by solvent casting method. The formulated films were evaluated for various physico-chemical tests. The prepared Glimepiride buccal films were optimized based upon their physicochemical characteristics and based on the results, batch F6 containing polymer combination of Carbopol 934 and HPMC K4M respectively of 25 mg and 10 mg was investigated as better formulation amongst all formulation. It shows good mucoadhesive time, swelling property and in-vitro drug release. The accelerated stability studies of developed optimized formulations for the 3 months
were also found to be stable. As an extension of this work pharmacokinetic studies, in-vivo studies on higher animals and controlled clinical studies on human beings will be carried out in future.

ACKNOWLEDGEMENT

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For Correspondence
Ashwini S. Nile
Email: ashwini.nile5@gmail.com