INTRODUCTION

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere biological surface for an extended period of time. Among the various routes of drug delivery the oral route is perhaps the most preferred by patients and clinicians alike. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal (GI) tract, that prohibit oral administration of certain classes of drugs, especially peptides and proteins. Consequently, other absorptive mucosas are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities) offer distinct advantages over peroral administration for systemic effect. These advantages include possible bypass of first-pass effects and avoidance of presystemic elimination within the GI tract.

The buccal region of oral cavity is an attractive site for the delivery of drugs owing to the ease of the administration. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and trans-mucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, where as the second case involves drug absorption through the mucosal barrier to reach the systemic circulation.

Mucoadhesive drug delivery systems

Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time. The ability to maintain a delivery system at a particular location for an extended period of time is an important consideration for drug delivery systems. In the second case involves drug absorption through the mucosal barrier to reach the systemic circulation.

MATERIALS &METHODS

Materials

Repaglinide was provided as sample from Swapnoor Laboratories Aurangabad, HPMC K100M, Chitosan, dextrose, mannitol, ethyl cellulose.
Table 1: Ingredient used in formulation.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Name of ingredients</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>1</td>
<td>Repaglinide</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>HPMC K 100 M</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Chitosan</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>Dextrose</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>Mannitol</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Ethyl cellulose</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Preformulation studies

Preformulation studies on the obtained sample of drug for identification and compatibility studies were performed.

Characterization of the Drug

Organoleptic properties

The sample of Repaglinide was studied for organoleptic properties such as colour, odour and appearance.

Melting point

The melting points of Repaglinide were determined by melting point apparatus. Observed value was compared with the reported value.

Drug excipient compatibility study

Drug excipient compatibility was performed by liquid Fourier Transform infrared. It was performed by mixing drug with excipient in equal proportion and then IR spectrum was noted for mixture using NaCl cell. Small amount of the mixture was placed on the sample cell, the cell was then filtered in sample holder, spectra were scanned over a frequency range 4000-400cm⁻¹ with FTIR instrument and the spectral analysis were done.

Preparation of Mucoadhesive buccal tablet (By Direct compression method)

1. Weighing of ingredients
2. Milling of drug and Excipients
3. Mixing of drug and Excipients
4. Tablet compression

EVALUATION OF MUCOADHESIVE BUCCAL TABLETS

Hardness test

Hardness test was conducted for three tablets from each batch and average values were calculated.

Weight variation test

Weight variation test was performed for ten tablets from each batch using an electronic balance and average values were calculated.

Table 2: Percentage deviation in weight variation

<table>
<thead>
<tr>
<th>Average weight of a tablet</th>
<th>Percentage deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 mg or less</td>
<td>10</td>
</tr>
<tr>
<td>More than 130 mg and less than 324 mg</td>
<td>7.5</td>
</tr>
<tr>
<td>324 mg or more</td>
<td>5</td>
</tr>
</tbody>
</table>

Thickness

The thicknesses of buccal tablets were determined using digital micrometer (Digital Caliper, Aerospace, India). Ten individual tablets from each batch were used and the average thickness was calculated.

Friability test

Friability of twenty randomly selected tablets from each formulation were determined by using the Roche type friabilator.

In vitro drug release for Repaglinide tablet

The drug release profile was studied using USP dissolution testing apparatus method II using a paddle at 50 rpm 900ml dissolution fluid, pH 6.8 phosphate buffer, was used and a temperature of 37 ±0.5°C was maintained. 5ml aliquots at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12 h respectively were pipette out and the same volume was replaced with pH 6.8 phosphate buffer. Absorbance was measured at λmax282nm and from which percentage of Repaglinide was calculated using calibration curve.

Table 3: In vitro drug release studies details

<table>
<thead>
<tr>
<th>Apparatus used</th>
<th>USP Type II dissolution test apparatus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution medium volume</td>
<td>Phosphate buffer pH 6.8</td>
</tr>
<tr>
<td>Temperature</td>
<td>37± 0.5°C</td>
</tr>
<tr>
<td>Speed of basket</td>
<td>50 rpm</td>
</tr>
<tr>
<td>Sampling intervals</td>
<td>1 Hrs</td>
</tr>
<tr>
<td>Sample withdraw</td>
<td>5 ml</td>
</tr>
<tr>
<td>Absorbance measured</td>
<td>282 nm</td>
</tr>
</tbody>
</table>
In vitro mucoadhesive strength

In vitro mucoadhesive strength of tablet was measured with goat oral mucosa, using a modified physical balance. On one side of the balance, a rubber closure tied with thread was attached and on other side empty polythene bag was attached. Goat oral mucosa was obtained from a local slaughter house and stored in a phosphate buffer pH 6.8 upon collection. The experiments were performed within 3 h of collection of oral mucosa which has been separated from sheep stomach. The goat stomach mucosa was fixed to the opening of the glass vial with thread and then placed in a beaker, well packed. Phosphate buffer pH 6.8 was added into the beaker up to the upper surface of the buccal mucosa to maintained oral mucosal viability during the experiment. The tablet was sticked to the rubber closure with cyanacrylate glue, then the beaker was raised slowly until contact between goat oral mucosa and tablet was established. A preload of 5 gm was placed on the clamp for 5 min (preload time) to establish adhesion bonding between tablet and goat oral mucosa. The preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp and water was then added in the polythene bag by pipette in drop-wise manner, at a constant rate. The weight of water required to detach tablet from stomach mucosa was noted as in vitro mucoadhesive strength, and these experiments were repeated with fresh mucosa in an identical manner. The modified physical balance for in vitro mucoadhesive strength determination consisting of polythene bag (on one side) and rubber closure for attachment of tablet (on other side).

Swelling Study

Buccal tablet are weighed individually (W1) and placed separately in petri dishes containing phosphate buffer pH 6.8 for 8 hrs at regular interval of time (1, 2, 4, 6 and 8 hr) and The tablet are removed from the petri dishes and excess surface water is removed using filter paper. The tablet are weighed (W2) and swelling index (SI) is calculated as follows

\[ SI = \frac{W2-W1}{W1} \]

Drug content uniformity

Ten tablets were accurately weighed and powder crushed in a glass pestle mortar. An accurately weighed amount equivalent to 5 mg of pure drug was taken, and the assay was performed UV spectrophotometer.

Optimization by 3² factorial designs:

Optimization is the key parameter in the development of any product factorial designs used to evaluate two or more factors simultaneously interactions can be determined in the factorial design. A study in which two factors and three levels are involved is called as 3² factorial design. For the present work 3² factorial design selected and 2 factors were evaluated at three possible levels by formulating all possible 9 formulation combination which are shown in table 3.

Table 4: design summary.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Name</th>
<th>Unit</th>
<th>Type</th>
<th>Min.</th>
<th>Max.</th>
<th>-1 actual</th>
<th>+1 actual</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>HPMC K100M</td>
<td>%</td>
<td>Numeric</td>
<td>15</td>
<td>25</td>
<td>-1.00</td>
<td>1.00</td>
<td>40</td>
<td>12.18</td>
</tr>
<tr>
<td>B</td>
<td>Xanthan Gum</td>
<td>%</td>
<td>Numeric</td>
<td>15</td>
<td>25</td>
<td>-1.00</td>
<td>1.00</td>
<td>40</td>
<td>12.18</td>
</tr>
</tbody>
</table>

HPMC K100M and Chitosan are independent variable used in the formulation. They are mucoadhesive polymer to increase the residence time of formulation in oral cavity and also show their effect on mucoadhesive strength, swelling index, in vitro drug release.

Independent variable

X1= HPMC K100M
X2= Xanthan gum

Dependent variable

Y1= Drug release
Y2= Swelling index
Y3= Mucoadhesive strength

In-vitro Drug Release Kinetic Study

Zero Order Kinetics

A Zero order release would be predicted by the following equation,

\[ Qt=Q0-K_0t \]

Where

\[ Qt=\text{Amount of drug release dissolved in time } t \]

\[ Co=\text{Initial amount of drug concentration in solution.} \]

\[ K_0=\text{Zero order rate constant}. \]

When the data were plotted as cumulative % drug release versus time, if the plot is linear then data obeys zero order kinetics with slope equal to \( K_0 \). This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First Order Kinetics:

A first order release would be predicted by the following equation

\[ \log Qt=\log Q0-Klt/2.303 \]

Where,

\[ Qt=\text{Amount of drug released in time } t \]

\[ Co=\text{Initial amount of drug concentration in solution.} \]

\[ Klt=\text{first order rate constant} \]

When data were plotted as log cumulative% drug remaining versus time yields a straight line indicating that the release
follows first order kinetics. The constant $K$ can be obtained multiplying slope values.

**Higuchi’s Model:**

Drug release from the matrix device by diffusion has been described by Higuchi’s diffusion equation

$$Ft=Q=VD5/T(2C-5Cs)Cst$$

Where,
- $Q$ = Amount of drug release dissolved in time $t$.
- $C_0$ = diffusion coefficient of drug in the release matrix.
- $Cs$ = Solubility of drug in the matrix.
- $S$ = porosity of matrix
- $t$ = Tortuosity
- $T$ = Time (h)

The equation may be simplified then the equation becomes,

$$Ft=Q=KhX t^{1/2}$$

Where,
- $Kh$ = Higuchi dissolution constant

When data were plotted according to this equation, i.e. cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

**Peppas-Korsmeyer Equation**

In 1983 Korsmeyer et al. developed a simple, semiempirical model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time ($t$)

$$At/Ao=Kt/n$$

Where,
- $K$ = Constant
- $n$ = Release
- $t$ = Time
- $At$ and $Ao$ = Absolute cumulative amount of drug released at times.

This is used when the release mechanism is not well known or when more than one type of a release phenomenon could be involved.

**RESULT AND DISCUSSION**

**Preformulation study**

**Identification and Characterization of the Drug**

**Organoleptic Properties**

The organoleptic properties of Repaglinide such as colour, appearance, odour was observed visually

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reported value</th>
<th>Observed value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Crystalline</td>
<td>Crystalline</td>
</tr>
<tr>
<td>Colour</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Odour</td>
<td>Odourless</td>
<td>Odourless</td>
</tr>
</tbody>
</table>

**Melting Point**

The melting point was determined by melting point apparatus and the melting point was found to be

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Point</td>
<td>130-131°C</td>
<td>128-132°C</td>
</tr>
</tbody>
</table>

**Solubility**

Solubility of Repaglinide was checked in various solvents

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Solvent</th>
<th>Descriptive term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methanol</td>
<td>Soluble</td>
</tr>
<tr>
<td>2</td>
<td>Water</td>
<td>Insoluble</td>
</tr>
</tbody>
</table>
DRUG EXCIPIENTS COMPATABILITY STUDY

Infra red spectrum

The FTIR spectrum of pure Repaglinide showed peaks in wave numbers (cm⁻¹) which corresponds to the functional group present in the structure of the drug. FT-IR spectrum of Repaglinide is shown in figure 1.

Fourier transform infra-red spectroscopy (FTIR)

Infra-red spectra of drug and polymers showed matching peak with the drug spectra. The data obtained from the IR spectra showed no evidence of the interaction between the drug and the polymer studies. All the major characteristics peaks of the drug were present in the drug polymer combination spectra which indicate compatibility of drug with the polymers.

Drug + HPMC K100M

Drug + Chitosan
Differential Scanning Calorimetry

Thermal analysis of drug was carried out using DSC. The Differential Scanning Calorimetry curve of repaglinide profiles a sharp exothermic peak at 134°C corresponding to its melting, and indicating its crystalline nature and purity of sample. The DSC thermogram is shown in Figure 4.

Figure 4: DSC Thermogram of Repaglinide

PRE-COMPRESSION PARAMETERS

Table 8: Pre compression parameters for Mucoadhesive buccal tablet

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (°) Mean ±S.D*</th>
<th>Bulk density(g/ml) Mean ±S.D*</th>
<th>Tapped density (g/ml) Mean ±S.D*</th>
<th>Carr’s index (%) Mean ±S.D*</th>
<th>Hausner’s ratio Mean ±S.D*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33.97±1.71</td>
<td>0.39±0.015</td>
<td>0.45±0.015</td>
<td>13.33±1.45</td>
<td>1.15±0.020</td>
</tr>
<tr>
<td></td>
<td>34.59±0.79</td>
<td>0.38±0.010</td>
<td>0.43±0.010</td>
<td>11.62±1.45</td>
<td>1.10±0.013</td>
</tr>
<tr>
<td></td>
<td>33.40±0.86</td>
<td>0.36±0.005</td>
<td>0.41±0.010</td>
<td>12.19±0.94</td>
<td>1.13±0.011</td>
</tr>
<tr>
<td></td>
<td>30.46 ±0.83</td>
<td>0.37±0.006</td>
<td>0.41±0.016</td>
<td>09.75±1.63</td>
<td>1.10±0.008</td>
</tr>
<tr>
<td></td>
<td>30.71±0.60</td>
<td>0.37±0.011</td>
<td>0.42±0.016</td>
<td>09.75±1.63</td>
<td>1.10±0.008</td>
</tr>
<tr>
<td></td>
<td>32.82±1.05</td>
<td>0.38±0.008</td>
<td>0.42±0.008</td>
<td>09.52±1.28</td>
<td>1.10±0.016</td>
</tr>
<tr>
<td></td>
<td>29.74±1.03</td>
<td>0.37±0.009</td>
<td>0.42±0.008</td>
<td>11.90±0.86</td>
<td>1.13±0.021</td>
</tr>
<tr>
<td></td>
<td>31.47±0.90</td>
<td>0.37±0.010</td>
<td>0.43±0.009</td>
<td>13.95±1.50</td>
<td>1.16±0.020</td>
</tr>
<tr>
<td></td>
<td>31.76±1.22</td>
<td>0.38±0.013</td>
<td>0.44±0.010</td>
<td>13.63±0.99</td>
<td>1.15±0.015</td>
</tr>
</tbody>
</table>

*n=6

POST COMPRESSION PARAMETERS

Table 9: Post compression parameters for Mucoadhesive buccal tablet

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (Kg/cm2)*</th>
<th>Thickness (mm)*</th>
<th>Friability (%)*</th>
<th>Weight variation (mg)*</th>
<th>pH*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.9±0.11</td>
<td>3.21±0.11</td>
<td>0.89±0.023</td>
<td>248±1.04</td>
<td>6.8±0.09</td>
</tr>
<tr>
<td></td>
<td>5.8±0.12</td>
<td>3.25±0.10</td>
<td>0.82±0.014</td>
<td>252±1.41</td>
<td>6.6±0.11</td>
</tr>
<tr>
<td></td>
<td>5.6±0.10</td>
<td>3.22±0.08</td>
<td>0.40±0.017</td>
<td>247±1.47</td>
<td>6.7±0.08</td>
</tr>
<tr>
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<td>5.4±0.12</td>
<td>3.20±0.14</td>
<td>0.40±0.034</td>
<td>253±1.04</td>
<td>6.6±0.10</td>
</tr>
<tr>
<td></td>
<td>5.8±0.10</td>
<td>3.25±0.11</td>
<td>0.60±0.299</td>
<td>250±1.94</td>
<td>6.8±0.11</td>
</tr>
<tr>
<td></td>
<td>6.0±0.11</td>
<td>3.20±0.11</td>
<td>0.40±0.021</td>
<td>248±1.47</td>
<td>6.7±0.14</td>
</tr>
<tr>
<td></td>
<td>6.0±0.14</td>
<td>3.24±0.21</td>
<td>0.56±0.026</td>
<td>250±1.72</td>
<td>6.8±0.12</td>
</tr>
<tr>
<td></td>
<td>5.7±0.14</td>
<td>3.21±0.11</td>
<td>0.44±0.014</td>
<td>247±1.41</td>
<td>6.8±0.10</td>
</tr>
<tr>
<td></td>
<td>5.9±0.13</td>
<td>3.19±0.11</td>
<td>0.40±0.026</td>
<td>246±1.60</td>
<td>6.7±0.08</td>
</tr>
</tbody>
</table>

Drug content

Figure 5: Graphical presentation of drug content
Swelling study

The swelling index of Repaglinide buccal tablet for 8 hrs. The water uptake nature of the polymer is one of the important properties that affect the onset of swelling. Swelling index increases with increases concentration of the HPMC K100M and xanthan gum. The formulation F7 possessing highest swelling index.

![Swelling index graph](image1)

Figure 6: Graphical Presentation of swelling index

Mucoadhesive strength

The highest bioadhesion strength was possessed by the formulation containing HPMC K100 M and Xanthan gum. Increases in the concentration of HPMC K100 M and Xanthan gum increases bioadhesion strength of the formulation.

![Mucoadhesive strength graph](image2)

Figure 7: Graphical presentation of Mucoadhesive strength

In-vitro dissolution study

In-vitro drug Release Studies of Repaglinide buccal tablets were determined using USP type II apparatus. The drug release was found to vary according to the ratio of mucoadhesive polymers. The formulation F7 showed the optimum drug release 96.21% at the end of 12 hrs containing HPMC K100M and xanthan gum.

![In-vitro drug release graph](image3)

Figure 8: Graphical presentation of In-vitro drug release
Optimization

A 3² full factorial design was selected and 2 factors were evaluated at 2 levels, respectively. The percentage of HPMC K100M (X1) and Xanthan Gum (X2) were selected as independent variables and dependent variables drug release, swelling index, mucoadhesive strength. The data obtained were treated using design expert software and analyzed statistically using analysis of variance (ANOVA).
Figure 15: Counter plot showing effect of HPMC K100M and Xanthan Gum on mucoadhesive strength

From design expert optimum batch of HPMC K100M and Xanthan Gum was found to be optimized. From this data F7 was selected as optimized formulation.

**Kinetic Study**

In the present study, the drug released mechanism from all formulation and evaluation of mucoadhesive tablet formulation different kinetic models was analyzed using factorial design batches followed zero order, first order model kinetic, Highuchi and Korsemeyer’s Peppas model kinetics.

<table>
<thead>
<tr>
<th>Table 10: R² values of Korsemayer’s peppas model kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
</tr>
<tr>
<td>R²</td>
</tr>
<tr>
<td>N Value</td>
</tr>
</tbody>
</table>

The classical zero order released curved was found to be linear the curve plotted according to first order and Highuchi were also found to be linear respectively. For the Korsemeyer’s Peppas released curves r² was found to be ≥ 0.90 for all formulation and n value was found to be ≥ 0.5 which indicate that all the formulation show anomalous or non-fickian diffusion. The drug release occurs probably by diffusion, erosion and dissolution follows.

**Stability studies of Mucoadhesive buccal tablet of Repaglinide**

<table>
<thead>
<tr>
<th>Table 11: Stability study of optimized formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr. No.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
</tr>
</tbody>
</table>

Optimized formulation F₇ at 25 °c temperature was found to be stable up to 2 months. There was no significant change in appearance, drug release and drug content.
CONCLUSION

It was planned in this investigation to formulate and evaluate mucoadhesive buccal tablet of Repaglinide to release the drug in buccal cavity for extended period of time in order to avoid first pass metabolism to reduce the dosing frequency and to improve the patient compliant. Experiments were conducted to investigate the influence of polymer like HPMC K100M and xanthan gum bioadhesion strength and release kinetic of mucoadhesive tablet of Repaglinide. In vitro dissolution studies were conducted in apparatus II at 50 rpm for 12 hr. Drug content of all formulation were found to be more than 96.55%. The pH of all mucoadhesive formulation was in between 6.7 to 6.8. In vitro drug release result of all the formulation were conducted for 12 hrs of all tablet formulation F1 -F9. The formulations F7 were taken as an optimized batch. It can be seen that by increasing the concentration of HPMC K100M and xanthan gum in the formulation, the drug release rate was found to be increased. The in vitro release kinetic indicate that all the formulation show anomalous or non-fickian diffusion. The drug release occurs probably by diffusion, erosion and dissolution follows. The data was statically analyzed and mechanism of release kinetic studied. All the studies were conducted at least 6 times and average was computed and tabulated.

ACKNOWLEDGEMENT

The authors are thankful to the principal and management of Loknete Dr. J. D. Pawar College of Pharmacy Manur, for providing necessary facilities to carry out this work.

CONFLICT OF INTERESTS

Declared None.

REFERENCES

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