**ABSTRACT**

The objective of this study is to achieve the controlling dissolution rate of Metformin HCl, a freely water soluble antidiabetic drug. Solid dispersions microcapsules were prepared using solvent evaporation method which enclosed preparation of a uniform dispersion of Metformin HCl in (Hydroxy propyl methylcellulose k100, Ethyl cellulose, Eudragit RL PO, RS PO & Compritol 888 ATO). A two-factor, General factorial statistical design was used to quantify the effect of polymer type (X1) and drug: polymer ratio(X2) on the release profile. Where polymer type and drug: polymer ratio were selected as independent variables, while Y1 (cumulative drug release after 1 hr.) and Y2 (cumulative drug release in 3 hrs.), Y3 (cumulative drug release in 10 hrs.), Y4 (angle of repose) and Y5 (Hausern ratio) were selected as dependent variables. The solid dispersions were characterized for their in vitro-release rate. The optimized formulation was further characterized by Drug scanning calorimetry, infrared spectrophotometry, X-Ray Diffractometer and SEM analysis. A convenient statistical model was made and a significantly controlled release rate was exhibited. The optimized formulation was investigated by DSC, XRD, FTIR and SEM data which showed the crystalline nature of Metformin HCl in a solid dispersion, the statistical model helped us to recognize the effects of formulation variables on the dispersion.

**Keywords:** Metformin HCl, Solid dispersion, controlled release, factorial design, HPMC k 100, Ethyl cellulose, Eudragit RL, RS & Compritol ATO 888.

**INTRODUCTION**

Controlled drug delivery is one which delivers the drug at a predetermined rate and controls release rate that maintain uniform blood level for a specified period of time. Controlled release drug delivery utilizes drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time. Such systems are preferred over traditional methods of drug delivery due to numerous advantages including modifying of drug release rates, protection of fragile drugs and improve patient comfort and compliance 1. Solid dispersion methods have been used widely in a various formulation to enhance dissolution rate and bioavailability of poorly water soluble drugs 2, 3, 4, 5. Preparation of matrices with water insoluble and water swellable polymers using solid dispersion method is valuable in the production of controlled release products. Many studies have been reported in the literature for the preparation of controlled release system, using solid dispersion technique 6, 7. The controlled release solid dispersions generally prepared by any of the methods: by dissolving the ingredients in a solvent followed by evaporation or by melting the active and inert ingredient. The carriers which are used include (ethyl cellulose, hydroxyl propyl methylcellulose, compritol ATO888, and meth acrylic acid copolymers).

The structure of the solid dispersion is monolithic wherein the drug molecules uniformly dispersed and it has a great advantage of avoiding the risk of burst release concerning the reservoir type, controlled release preparations. Both synthetic and biologically derived (natural) polymers have been extensively fulfilled as biodegradable polymers. Biodegradation of polymeric biomaterials includes cleavage of hydrolytically or enzymatically sensitive bonds in the polymer leading to polymer erosion 8.

Metformin hydrochloride is an oral anti-hyperglycemic agent, an orally administered biguanide, which is widely used in the management of type II diabetes, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is (50 –60 %) with a short plasma half-life of (1.5 -4.5 h). An obstacle to the more successful use of Metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea 9. The target of this study is to formulate and evaluate of sustained release (SR) microcapsules of Metformin HCl that would maintain the plasma levels of the drug for eight to twelve hours which might be sufficient for once daily dosing of Metformin HCL. Administration of a sustained-release Metformin dosage form once daily could reduce the dosing frequency and improve patients compliance 10. The full factorial experimental design is one of the best tools.
to declare the effect of different variables on the parameters of any formulation.

A statistical model was developed to optimize the solid dispersions and a significantly controlled release rate and flow properties were declared with the optimized dispersion microcapsules.

**MATERIALS AND METHODS**

**Materials**

Metformin HCl was brought as a gift from Ferchem Srl Co., Milano (Italy), Eudragit RLPO, Eudragit RSPO were brought as a gift from Rohm pharma, GMBH (Germany), Hydroxy propyl methylcellulose. HPMC K100 and compritol ATO 888 were obtained from colorcon limited, Luna supplier. All of the other chemicals and solvents were of reagent grade.

**Methods**

**Preparation of solid dispersions**

Microcapsules were produced by solvent evaporation method\(^1\) by dispersing accurately weight quantities of Metformin HCl and polymers individually (ethyl cellulose 300 cps, Eudragit RLPO, Eudragit RSPO, compritol ATO 888 and HPMC K 100) dissolved at different ratios (1:1 to 1:4) in a solvent (combination of mixture dichloromethane: chloroform(1:1) with continuous stirring and evaporation in open air, subsequently the solid mass was pulverized and passed through sieve No 18, the sieved granules were stored at 25 °C in a well-closed container until use.

**Formulation Design**

General factorial design has 2 to 15 factors, each factor must have at least 2 levels and at most 100 levels, but the number of levels can be different for each factor. The number of runs is limited to 10000, thus there is no catalog of available designs. In this study general factorial design containing 2 independent variables evaluated, one of them X1(a type of polymer) at 5 levels (HPMC, EC, Eudragit RLPO, Eudragit RS PO and Compritol) and the other X2(drug-polymer ratio) at 4 levels(1:1, 1:2, 1:3 and 1:4). The experimental trials were performed at 20 combinations.

**Evaluation of Solid Dispersions**

**In-vitro Dissolution studies**

The dissolution rate of Metformin HCl was estimated for all formulations using USP type II with six rotating basket, speed 100 rpm (Mumbai, India)\(^2\) and the dissolution media utilized was 900 ml of HCl pH 1.2 for 2 hrs. then converted to phosphate buffer pH 6.8 at 37°C by adding 30 gm of Tri-sodium orthophosphate.12 H\(_2\)O\(^13\). At suitable intervals, 5 ml of each sample was taken and assayed at 232 nm by UV-visible spectrophotometer and replaced by fresh dissolution media.

![Figure 1: In-vitro release of Metformin HCL capsules containing drug Compritol](image)

ATO 888 microcapsules (1:1, 1:2, 1:3, 1:4)

| Figure 1 showing dissolution profile of Metformin HCL-compritol microcapsules at different ratios (1:1,1:2,1:3 and 1:4). The data were analyzed by MINI TAB SOFTWARE (version 17). Metformin HCL microcapsules were optimized based on the percentage drug release criteria test to confirm acceptance criteria of USP\(^14\) as follow: |
| Release at 1hr : 20 to 40% |
| Release at 3 hrs. : 45 to 65% |
| Release at 10 hrs. : Not less than 85% |

**Drug content and percent yield**

Metformin HCl content of microcapsules was determined by an extraction method\(^5\). Microcapsules equivalent to (50mg) were weighed accurately, crushed and added to Methanol (20 ml) in volumetric flask and make up the volume with 100 ml 0.1 N HCl. The solution is shacked well and filtered through whatman filter paper no 44 and 10ml of filtrate was taken out and diluted up to 100ml with 0.1 N HCl, again 2 ml was taken out and diluted up to 10 ml with 0.1 N HCl and absorbance was assayed spectrophotometrically at 232 nm against 0.1 N HCl as a blank, the percent yield of each formulation was also calculated.

**Characterization the physical properties of the produced Metformin HCl microcapsules**

Determination of Densities before and after tapping and true density, Hausner Ratio and Compressibility Percent of the produced Metformin HCl Microcapsules, as shown in table (1).
thermograms of the products were obtained from 30°C to 450°C in an atmosphere of nitrogen. The physical properties of the produce were recorded using Ph. powder X-ray diffractometer, Perkin-Elmer, USA Infrared spectra of drug or polymer alone and drug-polymer microcapsules were measured at Functional Group Region (4000-1500 cm⁻¹). For analysis, the disks were made by mixing a suitable amount of each sample with 200mg of KBr and compressing the mixture under high pressure. Each FTIR spectrum was obtained by averaging 16 scans at a resolution of 4 cm⁻¹.

**Table (1):** Physical properties of the produced Metformin HCl microcapsules

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>Angle of repose</th>
<th>Bulk Density</th>
<th>Tapped density</th>
<th>Hausner Ratio</th>
<th>Carries index %</th>
<th>Bulkiness</th>
<th>True density</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>34.94 ± 0.088</td>
<td>0.4530 ± 0.013</td>
<td>0.6353 ± 0.008</td>
<td>1.40 ± 0.025</td>
<td>28.70 ± 1.26</td>
<td>2.21 ± 0.066</td>
<td>1.66503 ± 0.007</td>
</tr>
<tr>
<td>F2</td>
<td>37.24 ± 0.110</td>
<td>0.3848 ± 0.013</td>
<td>0.4554 ± 0.009</td>
<td>1.18 ± 0.015</td>
<td>15.50 ± 1.29</td>
<td>2.60 ± 0.085</td>
<td>1.52353 ± 0.008</td>
</tr>
<tr>
<td>F3</td>
<td>25.66 ± 0.113</td>
<td>0.3346 ± 0.014</td>
<td>0.3766 ± 0.014</td>
<td>1.13 ± 0.015</td>
<td>11.15 ± 0.86</td>
<td>2.99 ± 0.125</td>
<td>1.39657 ± 0.014</td>
</tr>
<tr>
<td>F4</td>
<td>31.52 ± 0.166</td>
<td>0.3854 ± 0.013</td>
<td>0.4562 ± 0.011</td>
<td>1.18 ± 0.015</td>
<td>15.52 ± 1.00</td>
<td>2.60 ± 0.085</td>
<td>1.46703 ± 0.007</td>
</tr>
<tr>
<td>F5</td>
<td>30.96 ± 0.020</td>
<td>0.4452 ± 0.014</td>
<td>0.4907 ± 0.016</td>
<td>1.10 ± 0.006</td>
<td>9.27 ± 0.44</td>
<td>2.25 ± 0.070</td>
<td>1.48380 ± 0.007</td>
</tr>
<tr>
<td>F6</td>
<td>27.76 ± 0.130</td>
<td>0.4382 ± 0.014</td>
<td>0.5128 ± 0.013</td>
<td>1.17 ± 0.049</td>
<td>14.55 ± 0.63</td>
<td>2.28 ± 0.075</td>
<td>1.45863 ± 0.011</td>
</tr>
<tr>
<td>F7</td>
<td>70.65 ± 0.146</td>
<td>0.3470 ± 0.014</td>
<td>0.4477 ± 0.011</td>
<td>1.29 ± 0.012</td>
<td>22.49 ± 0.80</td>
<td>2.88 ± 0.075</td>
<td>1.27673 ± 0.010</td>
</tr>
<tr>
<td>F8</td>
<td>31.45 ± 0.070</td>
<td>0.4563 ± 0.013</td>
<td>0.5238 ± 0.012</td>
<td>1.15 ± 0.021</td>
<td>12.89 ± 0.58</td>
<td>2.19 ± 0.065</td>
<td>1.41507 ± 0.008</td>
</tr>
<tr>
<td>F9</td>
<td>27.35 ± 0.092</td>
<td>0.3647 ± 0.014</td>
<td>0.4634 ± 0.010</td>
<td>1.27 ± 0.025</td>
<td>21.30 ± 1.38</td>
<td>2.74 ± 0.105</td>
<td>1.48677 ± 0.007</td>
</tr>
<tr>
<td>F10</td>
<td>40.61 ± 0.102</td>
<td>0.3547 ± 0.014</td>
<td>0.4142 ± 0.011</td>
<td>1.17 ± 0.015</td>
<td>14.37 ± 1.08</td>
<td>2.81 ± 0.111</td>
<td>1.26730 ± 0.011</td>
</tr>
<tr>
<td>F11</td>
<td>35.83 ± 0.117</td>
<td>0.3240 ± 0.012</td>
<td>0.3948 ± 0.013</td>
<td>1.22 ± 0.006</td>
<td>17.93 ± 0.36</td>
<td>3.09 ± 0.110</td>
<td>1.18533 ± 0.009</td>
</tr>
<tr>
<td>F12</td>
<td>34.43 ± 0.122</td>
<td>0.3333 ± 0.012</td>
<td>0.3852 ± 0.013</td>
<td>1.16 ± 0.006</td>
<td>13.47 ± 0.30</td>
<td>3.00 ± 0.105</td>
<td>1.25257 ± 0.011</td>
</tr>
<tr>
<td>F13</td>
<td>35.85 ± 0.133</td>
<td>0.3185 ± 0.013</td>
<td>0.4046 ± 0.013</td>
<td>1.27 ± 0.015</td>
<td>21.28 ± 0.10</td>
<td>3.14 ± 0.076</td>
<td>1.52863 ± 0.011</td>
</tr>
<tr>
<td>F14</td>
<td>31.74 ± 0.137</td>
<td>0.3553 ± 0.011</td>
<td>0.3936 ± 0.011</td>
<td>1.11 ± 0.021</td>
<td>9.73 ± 1.33</td>
<td>2.82 ± 0.087</td>
<td>1.47453 ± 0.008</td>
</tr>
<tr>
<td>F15</td>
<td>29.75 ± 0.125</td>
<td>0.3100 ± 0.013</td>
<td>0.3752 ± 0.012</td>
<td>1.21 ± 0.015</td>
<td>17.38 ± 1.33</td>
<td>3.22 ± 0.131</td>
<td>1.44337 ± 0.007</td>
</tr>
<tr>
<td>F16</td>
<td>32.04 ± 0.070</td>
<td>0.3451 ± 0.013</td>
<td>0.4127 ± 0.010</td>
<td>1.20 ± 0.015</td>
<td>16.38 ± 1.20</td>
<td>2.90 ± 0.115</td>
<td>1.39300 ± 0.008</td>
</tr>
<tr>
<td>F17</td>
<td>45.01 ± 0.142</td>
<td>0.3844 ± 0.009</td>
<td>0.4236 ± 0.012</td>
<td>1.10 ± 0.015</td>
<td>9.25 ± 1.16</td>
<td>2.60 ± 0.060</td>
<td>1.57630 ± 0.010</td>
</tr>
<tr>
<td>F18</td>
<td>31.81 ± 0.619</td>
<td>0.3343 ± 0.012</td>
<td>0.4119 ± 0.011</td>
<td>1.232 ± 0.015</td>
<td>18.84 ± 0.85</td>
<td>2.99 ± 0.110</td>
<td>1.34393 ± 0.009</td>
</tr>
<tr>
<td>F19</td>
<td>42.73 ± 0.124</td>
<td>0.3266 ± 0.012</td>
<td>0.4041 ± 0.013</td>
<td>1.237 ± 0.015</td>
<td>19.18 ± 0.78</td>
<td>3.06 ± 0.117</td>
<td>1.38710 ± 0.013</td>
</tr>
<tr>
<td>F20</td>
<td>38.64 ± 0.111</td>
<td>0.3149 ± 0.010</td>
<td>0.4254 ± 0.010</td>
<td>1.35 ± 0.012</td>
<td>25.98 ± 0.61</td>
<td>3.18 ± 0.097</td>
<td>1.45843 ± 0.008</td>
</tr>
</tbody>
</table>

**Data Analysis**

The response values for this study are Y1 (cumulative drug release in 1 hr), Y2 hrs (cumulative drug release in 3 hrs), Y3 (cumulative drug release in 10 hrs), Y4 (angle of repose) and Y5 (Hausner ratio). The multiple regression analysis was made using MINI TAB 17 software. Interaction plots and Contour plots are obtained from designed experiments by Analysis of data of full factorial design using ANOVA. The response values are subjected to multiple regression analysis to show the relationship between the factors and the responses values.

**Formulations Optimization**

The optimized formulation was estimated by using software MINI TAB 17 and applying constraints on dependent variables. one optimized formulation is obtained. The optimized batch (s) was further investigated by DSC, FTIR, XRD, and SEM.

**Differential Scanning Calorimetry**

Differential Scanning calorimeter DSC60A, Shimadzu, Japan was used. Samples (10mg) were weighted and sealed in flat-bottomed aluminum pans, then heated from 30°C – 450°C in an atmosphere of nitrogen. The thermograms of the products were obtained with a thermal analyzer equipped with advanced computer software programs at a scanning rate of 10°C/min⁻¹.

**Fourier Transform Infrared Spectroscopy (FT-IR)**

Using FT-Infrared spectrophotometer, Perkin-Elmer, USA Infrared spectra of drug or polymer alone and drug-polymer microcapsules were measured at Functional Group Region (4000-1500 cm⁻¹). For analysis, the disks were made by mixing a suitable amount of each sample with 200mg of KBr and compressing the mixture under high pressure. Each FTIR spectrum was obtained by averaging 16 scans at a resolution of 4 cm⁻¹.

**Powder X-ray diffraction studies**

The X-ray diffraction patterns of the powdered samples were recorded using Philips X-ray diffractometer equipment model pw/1710 with copper tube anode target, voltage 40 kV, current 35 mA, scanning rate of 4°C. Samples (Metformin HCl, and microcapsules) were scanned over a range of 20 angles from 4000-70000 at an angular speed of 0.02° per second.

**Scanning Electron Microscopy**

Scanning electron microscopy was used to describe the shape and the surface characteristics of microcapsules. Samples mounted on an aluminum stub were under
reduced pressure. The sample assembly was placed in the microscope and vacuum was applied. The microcapsules were observed under SEM.

RESULTS AND DISCUSSION

Data Analysis

The responses were recorded and data was analyzed using ANOVA. The individual parameter was evaluated using F-test and a polynomial equation for each response was generated using Multiple Regression analysis. Final Equation in Terms of Coded Factors:

Response: angle of repose: (Y4)

\[
Y_4 = 36.423 - 3.249 X_1(1) + 3.811 X_1(2) + 0.386 X_1(3) - 4.074 X_1(4) + 3.126 X_1(5) - 0.925 X_2(1) - 2.590 X_3(2) + 4.522 X_2(3) - 1.007 X_2(4) + 6.028 X_1*X_2(1) + 6.656 X_1*X_2(2) - 12.040 X_1*X_2(1) - 2.600 X_1*X_2(2) - 2.250 X_1*X_2(3) - 7.783 X_1*X_2(2) - 8.530 X_2(3) + 6.395 X_1*X_2(3)
\]

Response: hauser ratio : (Y5)

\[
Y_5 = 1.18383 + 0.04033 X_1(1) - 0.05300 X_1(2) + 0.01867 X_1(3) - 0.05550 X_1(4)+ 0.04950 X_1(5) - 0.00050 X_2(1) + 0.00083 X_2(2) - 0.02517 X_2(3) + 0.02483 X_2(4) + 0.17967 X_1*X_2(1) - 0.04167 X_1*X_2(1) - 0.07233 X_1*X_2(1) - 0.06567 X_1*X_2(2) - 0.02700 X_1*X_2(2) + 0.10167 X_1*X_2(2) - 0.07567 X_1*X_2(3) + 0.00100 X_1*X_2(4) + 0.07133 X_1*X_2(5) - 0.03667 X_1*X_2(5) + 0.03933 X_1*X_2(3) - 0.07400 X_1*X_2(3) + 0.09450 X_1*X_2(4) - 0.02250 X_1*X_2(4) + 0.07350 X_1*X_2(4) + 0.04350 X_1*X_2(5) + 0.051950 X_1*X_2(5) - 0.000083 X_1*X_2(5) + 0.03517 X_1*X_2(5) + 0.09517 X_1*X_2(5)
\]

In ANOVA,values of "Prob > F" less than 0.05 indicate model terms are significant. In this case X1, X2, X1*X2 are significant terms.

The interaction plot of X1*X2 on Y1 showed that HPMC at level (1:1),and Eudragit RL at level(1:3) and compritol(1:4) showed the optimum release rate at 1 hr.(20-40%). Contour plot of X1*X2 on Y1 shows that HPMC allows different cumulative percent of drug released after 1 hr using different drug polymer ratio. at level (1:1) drug to polymer ratio above 80 % of drug released. Increasing ratio at (1:2,1:3) percent of drug released decreased to be between(60-80%).At (1:4) level decreased the percent of drug released to be (20-40%).

The interaction plot of X1*X2 on Y2 showing levels (compritol,EUD RL,and EUD RS) at a drug : polymer ratio (1:4)showing the optimized release rate at 3 hrs (45-65%).The contour plot of X1*X2 on Y2 showed that Eudragit RS allows percent of drug release less than 20 % after 3hrs in all drug polymer ratio.Ethylcellulose at drug- polymer ratio (1:1,1:2) allows percent of drug release (20-40%) after 3hrs. when increasing the ratio to (1:3,1:4) percent of drug released decreased to less than 20 %). Compritol at (1:1, 1:2, 1:3)drug-polymer ratio released percent of drug range (40-60%) when increasing the ratio to (1:4) drug release percent decreased.

The interaction plot fig(2) of X1*X2 on Y3 indicated that using HPMC at levels (1:2,1:3,1:4) and Eudragit RL at levels (1:2,1:2,1:3) and compritol (1:1,1:2,1:3,1:4) optimized the release after 10 hrs.

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In order to study Metformin HCl polymer interactions the analysis will depend on polymer characteristic thermal properties as follow:

![Figure 4: the thermogram of Metformin HCl-compritol 888 ATO Microcapsules](image)

The contour plot fig (4) showed a sharp endothermic peak, with a melting point at 69.635 °C because of its crystalline nature and associated fusion enthalpy 118.124 J/G.

The DSC thermogram of Metformin-compritol microcapsules (fig.4(b)) showed a sharp endothermic peak at 232.295°C of Metformin an endothermic peak at 78.851 of compritol. This slight change of melting points of both of the components may be related to the dilution factor.

**Fourier Transform Infrared Spectroscopy (FTIR)**

FTIR spectrums of Metformin HCl and Metformin HCl-compritol microcapsules were applied from which we found 1-Pure Metformin HCl (fig.5(a)) shows characteristic bands from different functional group at: (3373.9-3299.5) cm⁻¹ due to NH₃ group primary stretching vibrations, (3173.2) cm⁻¹ due to secondary stretching NH₃ group, (1631.1-1573.4) cm⁻¹ due to -C=N group stretching vibrations, and (1061,933.4) cm⁻¹ due to C-N stretching vibrations and -NH out of plane bending. These results are in good agreement with the finding of other authors on Metformin HCl.

2-Metformin HCl-compritol microcapsules (fig.5(b)) shows the presence of all characteristic peaks of Metformin HCl and decrease in the intensity of the characteristic Metformin HCl bands at (3372.3 cm⁻¹, 3174.7 cm⁻¹) and also at (1570 cm⁻¹), which may be due to the weak hydrogen bonding between the drug and the polymer.
**Powder X-ray diffraction studies**

X-ray diffraction studies were applied on Metformin HCl alone, polymer alone and drug loaded polymer.

1- X-ray diffraction pattern of pure Metformin HCl showed sharp numerous distinct peaks notably at 2θ angles, were 12.2°, 23.7°, 24.5°, 37.1° and 50°. This series of sharp and intense diffraction peaks were emphasized the crystalline state of pure Metformin HCl.

2- X-ray diffraction pattern of compritol ATO 888 shows two peaks at 21° and 23° due to lipid Polymorphism.

3- The X-ray diffraction pattern of drug loaded microcapsules prepared by solid dispersion using compritol ATO 888 showed all the intense peaks of both the drug and the polymer. The crystallinity of drug in the solid dispersion was less than that observed before preparation. But the pattern still showing the typical signals of Metformin HCl but the intensity is weakened as shown in fig (6).

**CONCLUSION**

In present study, The results of experimental study showed that the factors (polymer type and drug : polymer ratio) significantly affects the dependent variables, Y1(cumulative percent drug release in 1 hr.), Y2(cumulative percent drug release in 3 hrs.), Y3(cumulative percent drug release in 10 hrs.), Y4(angle of repose) and Y5(Hausner ratio). It was clear that the use of solid dispersions can control the drug release, which was achieved by dispersion in polymeric carriers, HPMC k100, Ethyl cellulose, Eudragit RLPO, Eudragit RSPO and Compritol ATO 888. On the basis of dissolution studies of formulations and goals applied the ratio of polymers and Metformin HCl required to control release of Metformin HCl was obtained and optimized using 2 factor general full factorial designs. The results of factorial design suggested only one optimized combination of the polymer by which maximum desirability obtained. The optimized batch was further studied by Drug scanning calorimetry, Infrared spectrophotometry, X-ray diffractometer and Scanning electron microscopy, which showed that Metformin HCl did not lose the crystalline nature. In conclusion: Solid dispersion of Metformin HCl was found to be a useful technique for controlling release.

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