ORAL CONTROLLED RELEASE METFORMIN HYDROCHLORIDE ION EXCHANGE RESINATE BEADS

Ajit S. Raghuwanshi¹, Ajay S. Raghuwanshi² and U. K. Jain²

¹Department of Chemistry, The University of Warwick, Coventry, UK
²Bhopal Institute of Technology & Science-Pharmacy, Bhojpur Road, Bhopal (MP)

E-mail of Corresponding author: ajitbpharm09@gmail.com

Abstract
Treating with ion exchange resin has chemically modified metformin hydrochloride to form an oral controlled release beads using ion-exchange resin sorption method. A strong cation exchange resin Amberlite IR 120 was utilized for the sorption of the drug and the drug resinate was evaluated for various physical and chemical parameters. The drug content and percentage drug release were determined spectrophotometrically at 233 nm. About 43% of drug was loaded in 4.5 h and in-vitro dissolution study showed 84% of drug release in 8 h. The drug-resinate complex was microencapsulated with a polymer Eudragit RS 100 to further retard the release characteristics. Further, the drug-resinate complex and microencapsulated drug resinate were suspended in a palatable aqueous suspension base and were evaluated for controlled release characteristic.

Keywords: Metformin HCl, Ion-exchange resin, Controlled release.

Introduction
Metformin hydrochloride (C₄H₁₁N₅.HCl) is used as oral hypoglycaemic drug from the biguanide class and used in the management of type 2 diabetes mellitus¹. Chemically, it is known as 2-(N, N-dimethylcarbamimidoyl) guanidine with a molecular weight of 165.62. It is white crystalline powder, hygroscopic, bitter in taste and odorless. Major action of metformin HCl lay in increasing glucose transport across the cell membrane in skeletal muscle ². It is soluble in water but insoluble in ether and chloroform. The pKa of metformin HCl is 2.8 and 11.51 and the melting range is 230-231 °C ³. Amberlite IR 120, a strong cation exchange resin is non-toxic and also active at entire pH range (0 to 14). Much of the research effort in developing novel drug delivery systems has centred on sustained or controlled release of drug from dosage forms. Most of the new peroral sustained release preparations are solid dosage forms, i.e. tablets or capsules. Only recently has attention been devoted to
liquid sustained release preparations which may be more palatable to pediatric patients\(^4\).

The drug resinate complex was prepared through batch preparation and also microencapsulated to further retard the drug release\(^5\). Drug-resinate complex and microencapsulated drug resinate (15% Eudragit RS 100) were then suspended in a palatable aqueous suspension base in order to make them for ready to use formulation.

**Preparation**

\[
\text{RESIN-SO}_3 + \text{Metformin HCl} = \text{HCl} + \text{ResinSO}_3\cdot\text{Metformin.H}
\]

**Exchange in body**

\[
\text{ResinSO}_3\cdot\text{Metformin.H} + \text{NaCl} = \text{Metformin.HCl} + \text{Resin.SO}_3\text{Na}
\]

A strong resin must be used to minimize exchange of drug by hydrogen ion, to avoid excessive drug release in the gastric fluid\(^6,7\).

**Material and Methods**

A strong cation exchange resin (Amberlite IR 120) was purchased from Merck limited Delhi. Metformin HCl was procured as a gift sample from Zydus Research Centre, Ahmedabad as gift sample and used as such. Demineralised water was used to prepare all the solutions. The resin in hydrogen form was evaluated for moisture content, particle size and cation exchange capacity.

Drug resinate can also be prepared through column but it requires more solvent so preparation of drug-resinate was tried by batch method\(^8\). Accurately weighted Metformin was dissolved in 100 ml demineralised water and Amberlite IR 120 was added in the 1:1 proportion. This mixture was stirred for 5 h on magnetic stirrer and filtered through Whatman filter paper. Drug loading was determined spectrophotometrically at 233 nm. The time required for maximum drug loading is shown in Fig-I. The drug-resinate was evaluated for drug content and *in vitro* drug release.

The drug-resinate was weighed accurately and placed in USP rotating basket method employing 900 ml of dissolution medium pH 1.2 for first 2 h and 7.2 pH for remaining 6 h maintained at 37±0.5°C. The speed of the basket was maintained at 50 rpm. The release pattern of drug-resinate was determined spectrophotometrically and results are shown in Fig-II\(^9\). To further retard the drug release, the resinate particles were coated with Eudragit RS 100 (5 – 25% w/w). Microencapsulation was carried out by solvent evaporation technique\(^10\).

The drug-resinate was stirred with polymer solution for 2 h. The solvent was
evaporated by continuous stirring on a water bath. Microencapsulated product was dried at 40 °C and evaluated for drug content and in vitro drug release. The results are given in table-I. The in vitro drug release from drug-resinate was significantly retarded after coating as shown in Fig-II.

Microencapsulated drug resinate beads obtained by coating the drug-resinate with 15% Eudragit RS 100 were selected for the formulation of suspension as it has shown a better sustained release profile.

Microencapsulated beads were formulated into aqueous suspension containing Xanthan gum (0.4% w/v) as suspending agent\textsuperscript{11}. The optimum formulation contained xanthan gum (0.4% w/v), sorbitol (40% v/v), sucrose (40% w/v), Tween 20 (0.1% v/v), and sodium methylparaben in a coloured and flavored aqueous base. The suspensions of uncoated drug-resinates and microencapsulated beads were prepared and their physicochemical parameters were compared. Compatibility of the ingredients with coated and uncoated drug resinate was also checked.

The suspension was evaluated for aesthetic appeal, pH, particle size analysis, wt/ml, sedimentation rate, redispersibility, viscosity and in vitro drug release pattern\textsuperscript{12}. The results are given in Table-2.

Leaching of the drug from the resinate complex into the aqueous suspension vehicle was also studied and shown as drug eluted in the vehicle.

**Results**

The process for preparing drug resinate was optimized with respect to methodology, drug resin proportion and time for sorption. Loading was tried by batch method, as efficient elution of the drug from column requires more solvent. The drug resin proportion of 1:1 achieved equilibrium in 4.5 h as shown in Fig-I and 43% w/w of drug loading was possible by this method. These drugs resinate released 84% of the drug in 8 h as shown in Fig-II.

**Discussion**

The uncoated metformin hydrochloride resin complex released the drug rapidly. To further retard the release drug-resinate complex was coated with Eudragit RS-100 (5-25%w/w). In the coated drug resinate the drug release was found to decrease from 74% to 53% in 8 h as shown in Fig-II.

Thus drug resinate complex has proved to be an efficient carrier for oral controlled release formulation of metformin hydrochloride.

**References**

1. Merck and Co. The Merck Index: an Encyclopedia of Chemicals, Drugs and Biological. 14 th ed. USA: Published
### Table-I: Evaluation of Drug Resinate Beads

<table>
<thead>
<tr>
<th>Test</th>
<th>Uncoated drug resinate beads</th>
<th>MDR 5% Eudragit</th>
<th>MDR 10% Eudragit</th>
<th>MDR 15% Eudragit</th>
<th>MDR 20% Eudragit</th>
<th>MDR 25% Eudragit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature</td>
<td>Free flowing</td>
<td>Free flowing</td>
<td>Free flowing</td>
<td>Free flowing</td>
<td>Free flowing</td>
<td>Cohesive, Lumpy</td>
</tr>
<tr>
<td>Drug Content (%w/w)</td>
<td>43.0</td>
<td>38.4</td>
<td>35.3</td>
<td>33.1</td>
<td>32.8</td>
<td>31.2</td>
</tr>
<tr>
<td>Particle Size (µm)</td>
<td>40-122</td>
<td>63-140</td>
<td>74-156</td>
<td>82-166</td>
<td>92-178</td>
<td>102-189</td>
</tr>
<tr>
<td>% in vitro drug release in 8 h</td>
<td>84</td>
<td>74</td>
<td>65</td>
<td>59</td>
<td>54</td>
<td>53</td>
</tr>
</tbody>
</table>

MDR: Microencapsulated drug resinate beads

### Table-II: Evaluation of Suspension of Drug Resinate Beads

<table>
<thead>
<tr>
<th>Evaluation Parameter</th>
<th>Uncoated drug resinate beads</th>
<th>MDR 15% Eudragit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Uniform</td>
<td>Uniform</td>
</tr>
<tr>
<td>Taste</td>
<td>Palatable</td>
<td>Palatable</td>
</tr>
<tr>
<td>pH</td>
<td>5.82±0.02</td>
<td>6.02±0.01</td>
</tr>
<tr>
<td>Viscosity (cps)</td>
<td>361</td>
<td>394</td>
</tr>
<tr>
<td>Sedimentation</td>
<td>0.93</td>
<td>0.97</td>
</tr>
<tr>
<td>Particle Size</td>
<td>40-122</td>
<td>82-166</td>
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<tr>
<td>Wt per mL</td>
<td>1.26</td>
<td>1.56</td>
</tr>
<tr>
<td>Redispersibility</td>
<td>Very Good</td>
<td>Very Good</td>
</tr>
<tr>
<td>Drug eluted in Vehicle</td>
<td>0.09%</td>
<td>0.38%</td>
</tr>
<tr>
<td>% <em>In vitro</em> Release</td>
<td>84</td>
<td>59</td>
</tr>
</tbody>
</table>

MDR: Microencapsulated drug resinate beads
Fig-I: Loading of metformin hydrochloride on Amberlite IR 120

Fig-II: *In vitro* release studies of drug resinate beads and microencapsulated drug resinate beads.