TRANSDERMAL PATCHES BASED ON SOLID LIPID NANOPARTICLES OF METFORMIN: A NOVEL DRUG DELIVERY

Navneet Sharma, Rakesh Kumar Sharma, Dharam Pal Pathak
DIPSAR, University of Delhi, Delhi, India 110054
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**Metformin Brief Introduction**: 

- **Metformin** is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes (NIDDM).
- Metformin causes few adverse effects, the most common is gastrointestinal upset & hypoglycaemia.
- Lactic acidosis (a buildup of lactate in the blood) can be a serious concern in overdose but otherwise, there is no significant risk.
- **MOA**: Metformin decreases glucose production in the liver, increases insulin sensitivity and enhances peripheral glucose uptake. It does not stimulate secretion of endogenous insulin.
- Metformin decreases hyperglycemia primarily by suppressing glucose production by the liver.
Formulations of Metformin:

Metformin IR (immediate release):
Strengths available: 500 mg, 850 mg, & 1000 mg tablets.

The liquid metformin is sold under the name Riomet. Each 5ml of Riomet is equivalent to the 500 mg tablet form of metformin.

Metformin SR (slow release) or XR (extended release):
Introduced in 2004.
It is available in 500 mg, 750 mg & 1000 mg strengths.

DEMERITS:
First pass effect.
Slow onset of action as compare to parenterals, liquid orals & capsules.
Difficult to swallow for terminally ill and geriatric patients.
Specific demerits of Metformin as a oral route

- Metformin has the potential to stimulate lactic acid production when renal excretion is decreased.
- Up to 20% of patients taking oral Metformin will experience the side effects such as anorexia, nausea, vomiting, abdominal discomfort and diarrhea.
- The effects are dose related however up to 5% will discontinue therapy due to the side effects.
- The 77% of patients taking metformin will also develop the Vitamin B12 deficiency.
- Metformin is absorbed over 6hrs. The bioavailability of the metformin is only 50-60% under fasting condition.
Solid Lipid Nanoparticles

- Emerging field of the lipid nanotechnology.
- Combine the advantages of lipid emulsion and polymeric nanoparticle systems overcoming the temporal and invivo stability issues.
- Typically spherical having particle size dia. Between 10 to 1000nm.
- Solid lipid core matrix that can solubilize lipophilic molecules.
- Advantages:-
  - Use of physiological lipids & the avoidance of the organic solvents.
  - Improved bioavailability.
  - Controlled released characteristics.
**Transdermal Drug delivery:**

Topically administered medicaments in the form of patches or semisolids to deliver drugs for systemic effects at a predetermined & controlled rate.

**MERITS:**
- Avoidance of the first-pass effect.
- Long duration of action
- Ease of termination of drug action, if necessary.

**Other transdermal Drugs:**
- Glipizide
- Glibenclamide
- 3. Hyoscine
- 4. Nitroglycerine
Materials & Methods:

- **Ingredients**
  - Polymethacrylic acid (polymer)
  - Propylene glycol (Penetration enhancer)
  - Soya lecithin (lipid base)
  - Metformin (5mg)
  - Methocel (film forming agent)
  - Acetone (Solvent)
  - Ethanol (Solvent)

- **Experimental Models**
  - Male Wistar rats (240 ± 20 gms)
  - Balb C Mice (20 to 30 gms)
Preparation Of Metformin – Solid lipid Nanoparticles (M-SLN) & Metformin transdermal patches:

**Preparation of Nanoparticles**

Metformin + water + acetone (*solution 1*)

Polymer & PEG dissolved in CHCl₃ along with Soya lecithin --- (*solution 2*)

(*solution 2 + solution 1*)

Dispersion + ethanol

*Mix*

removed by evaporation

Different batches of nanoparticles

**Transdermal Patch**

Polymer soaked in water for overnight addition of M-SLN

Mixed uniformly

Suspension casted on glass mould

Organic Solvent drying

Cut into small pieces
Particle size, Zeta potential & Surface morphology:

- Particle size determined by Photon correlation spectroscopy
  - Particle size of 200-245 nm was obtained.
  - Determined at a detection angle of 173 at 25 ºc.

- Scanning Electron Microscope:
  - Non aggregated microcapsules with spherical shape were obtained.

- Transmission Electron Microscope:
  - A Philips CM 10 TEM was used.
  - A conc. of 0.5% w/v of nanoparticle was sprayed on Formvar-coated Cu grids & air dried. M-SLP were spherical in shape.
Drug Content & FT-IR Analysis:

Drug content was done by ultrafiltration-centrifugation method

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug : Polymer ratio</th>
<th>Drug Content* (%)</th>
<th>Particle Size *(nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>68.32±0.02</td>
<td>12±8</td>
</tr>
<tr>
<td>F2</td>
<td>1:2</td>
<td>74.3±0.08</td>
<td>225±5</td>
</tr>
<tr>
<td>F3</td>
<td>1:3</td>
<td>80.83±0.03</td>
<td>237±9</td>
</tr>
<tr>
<td>F4</td>
<td>1:4</td>
<td>94.62±0.02</td>
<td>242±5</td>
</tr>
<tr>
<td>F5</td>
<td>1:5</td>
<td>78.96±0.04</td>
<td>203±4</td>
</tr>
</tbody>
</table>

* Average of three preparation ± S.D

FT-IR Analysis:

- Pure metformin & drug + polymer spectra were recorded.
**In-vitro studies:**

- **Drug content analysis**
  - Patches of specified area were weighed
  - dissolved
  - 100 ml ethanol
  - membrane filtration
  - Drug content analysed by HPLC

- **Ex-vivo permeation study**
  - Skin samples mounted on Franz diffusion cells with stratum corneum side-up
  - Receiver comp. filled with physiological saline (sink condition 37±0.5°C with 100rpm)
  - 3cm Metformin patch mounted on skin
  - sample collection
  - Filtration & analysed by HPLC.
**In-vivo studies:**

**Preparation of animals for studies:**

Male Wistar rats were used.

Animals were divided into 03 groups;

- **Group I** – Placebo patch (control) prepared by Methocel without nanoparticles.
- **Group II** – Metformin oral administration
- **Group III** - Transdermal patch with Metformin nanoparticles.

**Induction Of Diabetes:**

Induced by Streptozocin dissolved in 0.1 M citrate-citrate sodium buffer Ph 4.5 intraperitoneally in all 03 groups.

Blood samples were collected from tail vein to determine blood glucose levels.
<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Normal rats (mg/dl)</th>
<th>Diabetes rats (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Patch (Control)</td>
<td>Oral (2mg)</td>
</tr>
<tr>
<td>0</td>
<td>86.17±0.12</td>
<td>86.02±0.34</td>
</tr>
<tr>
<td>2</td>
<td>84.33±0.32</td>
<td>69.60±0.82</td>
</tr>
<tr>
<td>4</td>
<td>84.17±0.22</td>
<td>67.12±0.96</td>
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<tr>
<td>8</td>
<td>84.92±0.53</td>
<td>59.42±0.16</td>
</tr>
<tr>
<td>10</td>
<td>84.04±0.72</td>
<td>53.08±0.22</td>
</tr>
<tr>
<td>12</td>
<td>84.86±0.24</td>
<td>71.18±0.42</td>
</tr>
<tr>
<td>24</td>
<td>84.10±0.41</td>
<td>75.92±0.44</td>
</tr>
<tr>
<td>36</td>
<td>83.98±0.92</td>
<td>76.64±0.10</td>
</tr>
<tr>
<td>48</td>
<td>84.62±0.74</td>
<td>77.06±0.04</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. n=4. p<0.05.
-vivo evaluation of M-SLN Transdermal patches for biocompatibility:

- M-SLN Patches were subcutaneously applied on back of mice
- control group was also applied with same patch without M-SLN
- Histopathological changes were noted at application sites.
The text on the image reads:

Biocompatibility studies:

7th Day

A

7th Day

FT (fibrous tissues)

14th Day

B

CF (collagenous fiber)

21st Day

C

FT (fibrous tissues)

(100×, N neutrocyte; CF collagenous fiber; FT fibrous tissues)
M-SLN incorporated in transdermal patch possess marked hypoglycaemic activity & antihyperglycaemic activity.

Ex-vivo permeation studies predicted high cumulative amount of drug permeated by using nanoparticles made by polymethacrylic acid.

Histopathological studies confirm that M-SLN transdermal patches is biocompatible for use.

When prescribing transdermal Metformin, one advantage and key point is that the patient dose is generally only 10% of their oral dose. For ex. Instead of taking 500mg of metformin twice daily, a patient would apply 50mg topical to the inner wrists twice daily (10% of their oral dose).

To conclude, our results demonstrate the use of M-SLN in transdermal patches for the first time & show its therapeutic potential to be used as a cost effective, safe mode of drug delivery systems.
THANK YOU