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

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- Metformin & its formulations
- Transdermal Drug Delivery
- Preparation & characterisation
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Metformin Brief Introduction :

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

ormulations of Metformin :

Metformin IR (immediate release) :

Strenghts 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 parentrals, 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 decresed.
- 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 thrapy due to the side effects.
- The 77% of patients taking metformin will also develop the Vitamin B12 deficiency.
- Metformin is absorbed over 6hrs. The biavability of the metformin is only 50-60% under fasting condition.

Solid Lipid Nanoparticles

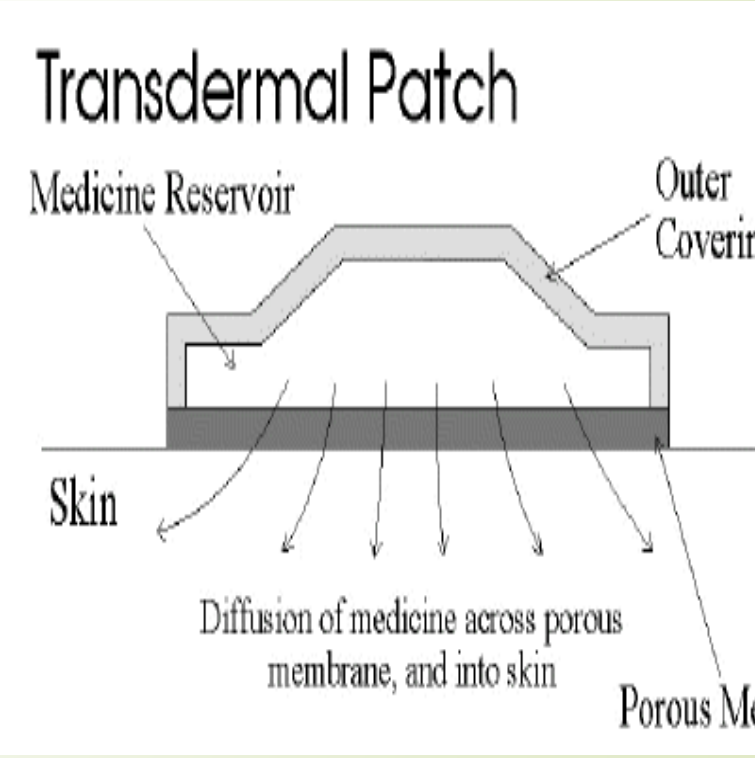
- Emerging field of the lipid nanotechnology.
- Combine the advantages of lipid emulsion and polymeric nanoparticl systems overcoming the temporal and *invivo* stability issues.
- Typically spherical having particle size dia. Between 10 to 1000nm.
- Solid lipid core matrix that can solubilize lipophilic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

ransdermal Drug delivery :

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

ERITS :

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



ther 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)

reparation Of Metformin – Solid lipid Nanoparticles (M-SLN) & Metformin transdermal patches :

Preparation of Nanoparticles

letformin + water + acetone *(solution 1)*

Polymer & PEG dissolved in $CHCl_3$

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 dryin

Cut into small pieces

article size , Zeta potential & Surface morphology :

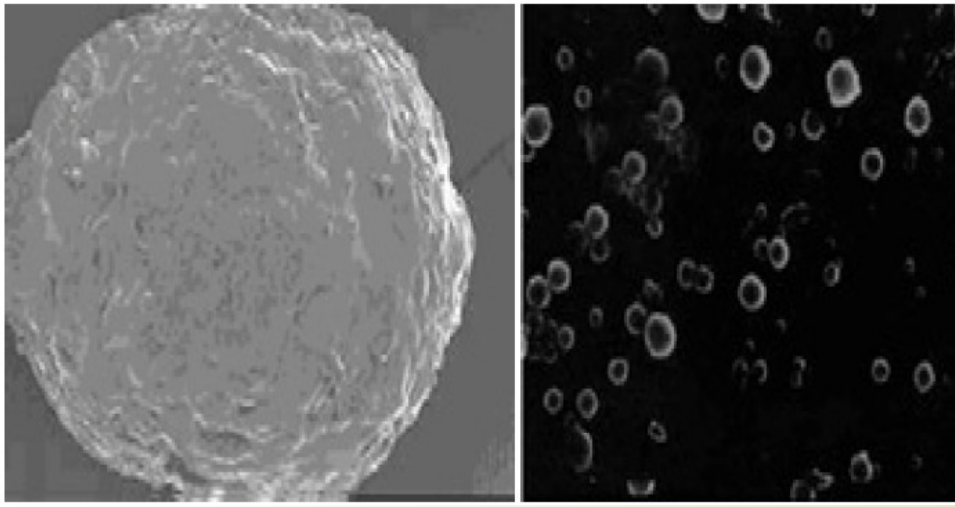
- Particle size determined by Photon correlation spectroscopy
- Particle size of 200-245 nm was obtained.
- Determined at a detection angle of 173 at 25 °c.

canning Electron Microscope :

- Non aggregated microcapsules
- with spherical shape were obtained.

ransmission Electron Microscope :

- A Philips CM 10 TEM was used.
- A conc. of 0.5% w/v of nanoparticle was sprayed on Formwar-coated Cu grids & air dried. M-SLP were spherical in shape.



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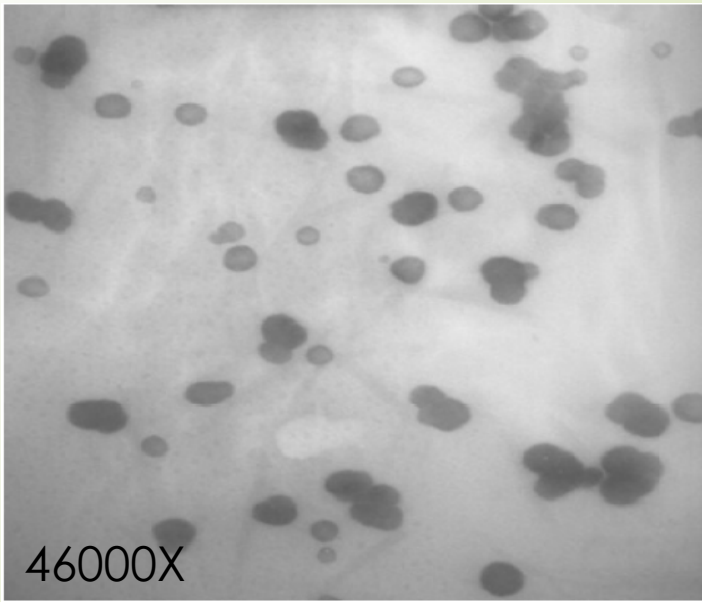


ug Content & FT-IR Analysis :

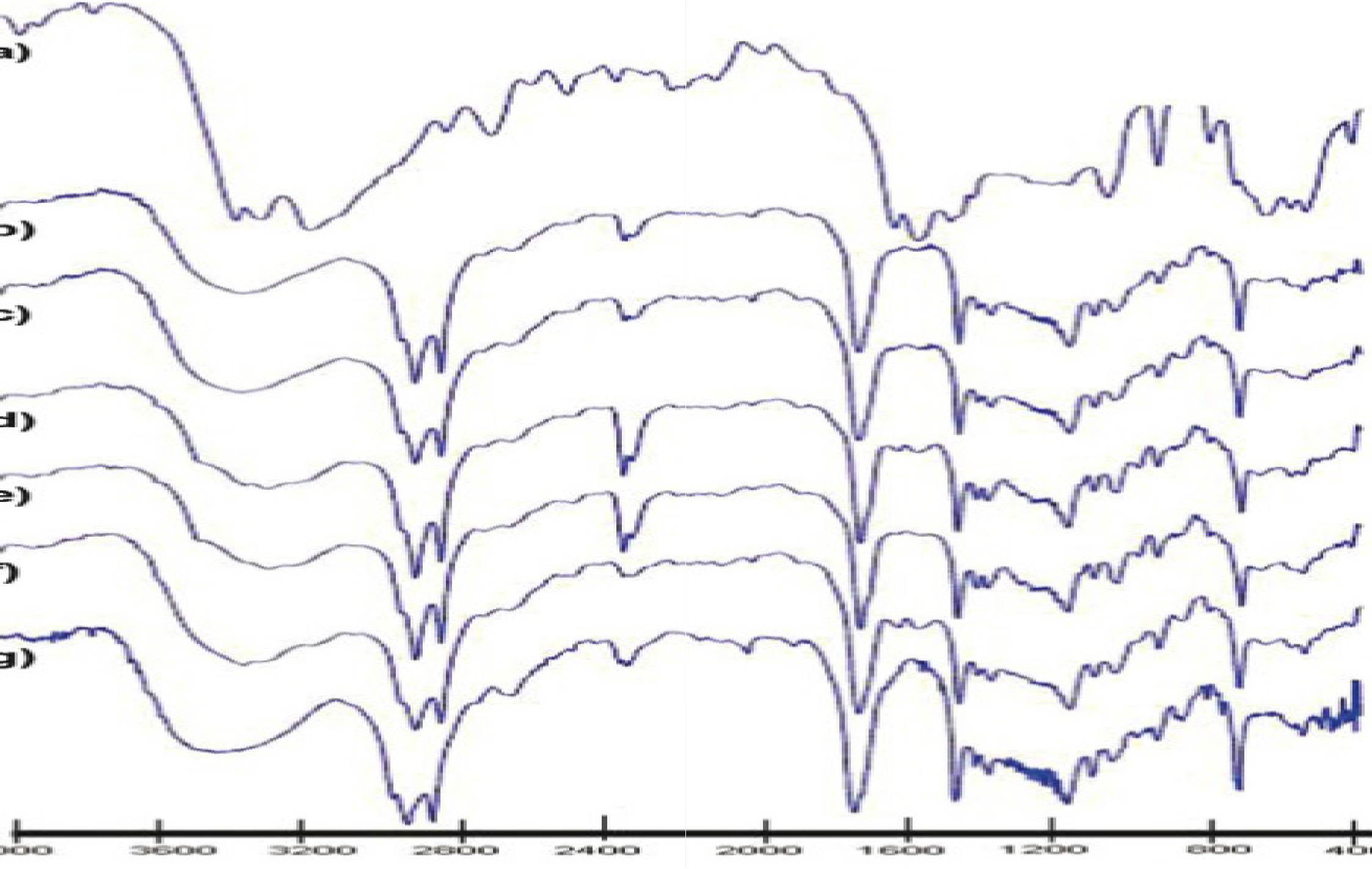
Drug content was done by ultrafiltration-centrifugation method

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

* Average of three preparation ± S.D

➢ FT-IR Analysis :

•Pure metformin & drug + polymer spectra were recorded.


a)
b)
c)
d)
e)
f)
g)
3600
3200
2800
2400
2000
1600
1200
800

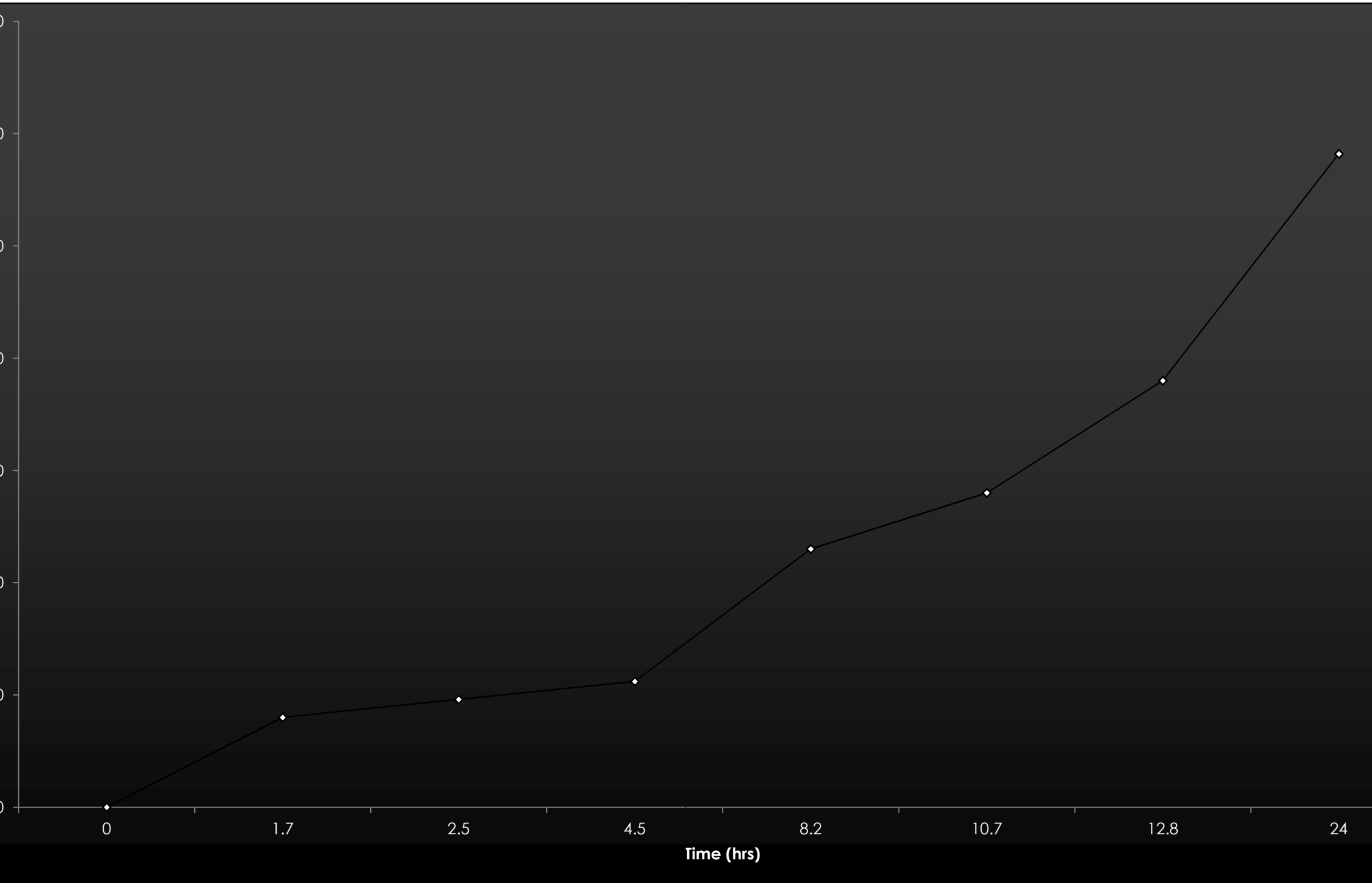
n-vitro studies :

rug 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 corneu side-up
- Receiver comp.filled with physiological saline (sink conditio
- 37±0.5ºC with 100rp
- 3cm Metformin patch mounted on sk
- sample collection
- Filtration & analysed by HPLC.


0
1.7
2.5
4.5
8.2
10.7
12.8
24
Time (hrs)

n-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.

nduction 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.

	Normal rats (mg/dl)			*Diabetes rats (mg/dl)*		
Time (hrs)	Placebo Patch (Control)	Oral (2mg)	M-SLN loaded patch	Placebo Patch (Control)	Oral (2mg)	M-SLN loaded patch
0	86.17±0.12	86.02±0.34	85.98±0.24	335.67±0.02	330.67±0.10	336.67±0.10
2	84.33±0.32	69.60±0.82	79.16±0.76	333.33±0.02	184.42±0.32	300.18±0.62
4	84.17±0.22	67.12±0.96	76.00±0.14	335.10±0.14	128.33±0.40	260.27±0.02
8	84.92±0.53	59.42±0.16	70.18±0.38	337.67±0.12	111.60±0.62	248.00±0.22
10	84.04±0.72	53.08±0.22	68.66±0.38	331.45±0.98	97.48±0.60	211.92±0.60
12	84.86±0.24	71.18±0.42	64.20±0.72	339.10±0.22	227.10±0.34	195.68±0.02
24	84.10±0.41	75.92±0.44	51.38±0.34	339.48±0.62	260.87±0.10	111.34±0.06
36	83.98±0.92	76.64±0.10	39.42±0.04	338.62±0.74	258.44±0.22	107.62±0.88
48	84.62±0.74	77.06±0.04	34.40±0.04	339.09±0.02	268.19±0.02	91.74±0.02

Values are expressed as mean ± SEM, n=4, $p<0.05$.

-vivo evaluation of M-SLN Transdermal patches for ocompatibility :

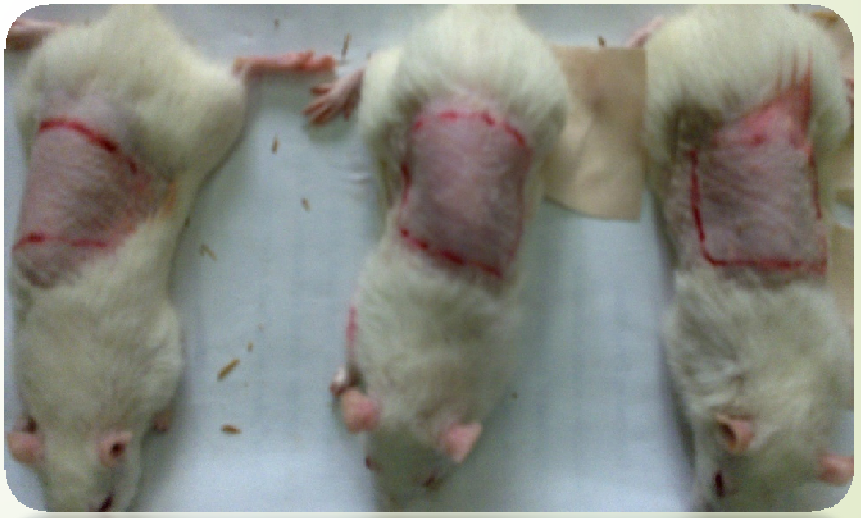
- M-SLN Patches were subcutaneously applied on back of mice

↓

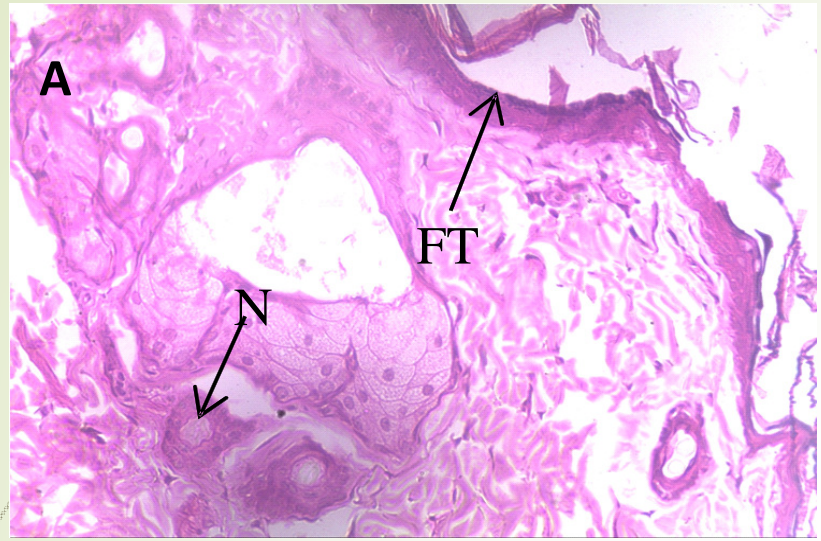
control group was also applied with same patch without M-SLN

↓

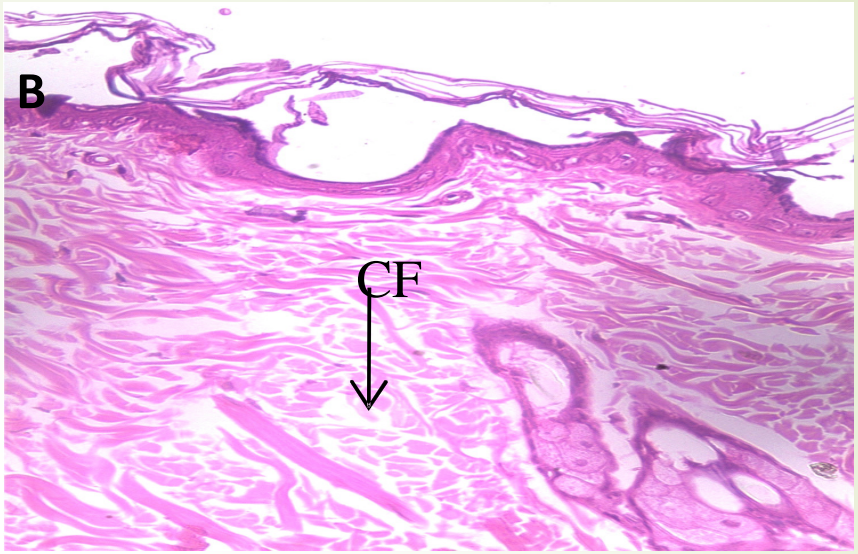
Histopathological changes were noted at application sites.



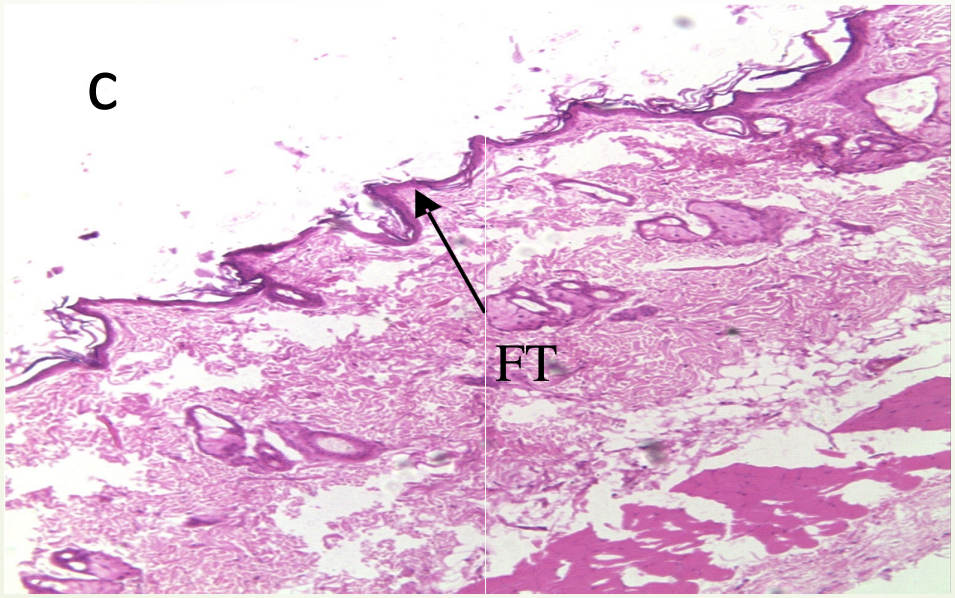
ocompatibility studies:-



7th Day



14th Day



21st Day

(100×, N neutrocyte; CF collagenous fiber; FT fibrous tissues)

ISCUSSION :

- 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 the patient dose is generally only 10% of their oral dose. For ex. Instead o taking 500mg of metformin twice daily, a patient would apply 50mg topic 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 c effective, safe mode of drug delivery systems.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