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FORMULATION OF HERBAL MEDICATED MONOLITHIC MATRICES USING EXTRACTS OF *AZADIRCHATA INDICA* (NEEM)

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ABSTRACT

The current research work was aimed with an objective to formulate Herbal medicated monolithic matrices using extracts of *Azadirchata indica* (Neem) & to evaluate therapeutic efficacy of prepared matrices by *in vitro* anti-inflammatory & antibacterial activity. Herbal medicated monolithic matrices using Methanollic extracts of *Azadirchata indica* (Neem) were developed with different concentrations of sodium CMC by solvent evaporation technique. Three transdermal patch formulations (F_1, F_2& F3) consisting different concentrations of Sodium CMC were prepared. All formulations carried Tween-80 as penetration enhancer and PEG-400 as plasticizer in water and methanol (1:1) solvent system. The prepared transdermal patches were evaluated for their physicochemical characteristics such as physical appearance, weight variation, thickness, folding endurance, percentage moisture absorption, percentage moisture loss, water vapour transmission, tensile strength. *In- vitro* anti-inflammatory activity of prepared transdermal matrices is observed by recording inhibition of protein denaturation. Antibacterial activity of the prepared patches is evaluated against pathogenic strain of Staphylococcus aureus.

KEYWORDS: Monolithic matrices, *Azadirachta indica* (Neem), Sodium CMC, Transdermal patches, etc.

1. INTRODUCTION

The potential of using the intact skin as the port of drug administration has been recognized for several decades as evidenced by the development of medicated plasters in china and Japan. This triggered the research curiosity of several biomedical scientists to evaluate the feasibility of transdermal delivery of systemically-effective drugs. The findings accumulated over the years have practically revolutionized the old concept of impermeable skin barrier and also motivated a number of pharmaceutical scientists to develop patch-type drug delivery systems for transdermal rate controlled administration of drugs for systemic medication as well as for topical administration of the locally acting drugs.[1]

"Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation".[2]

The transdermal delivery has gained importance in recent years. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, and decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.

Fig1.1: Transdermal Drug delivery Patches.

Formulations on skin can be classified into two categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneous micro vascular network, and the other exhibits local effects in the skin.[3] The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system.

The worldwide transdermal patch market approaches £ 2 billion, based on only ten drugs including Fentanyl, Nitroglycerin, Estradiol, Ethinyl Estradiol, Norethindrone Acetate, Testosterone, Clonidine, Nicotine, Lidocaine, Prilocaine, Scopolamine, Norelgestromin and Oxybutynin.[1,4,5] In a recent market report it was suggested that the growth rate for transdermal delivery systems will increase 12% annually.[6]

1.1. Advantages of TDDS[1, 8-10]

- Prevents the risk and inconvenience of intravenous therapy.
- Permits continuous zero-order drug administration and the use of drugs with short biological half-lives.
- Increases the bioavailability and efficacy of drugs, since it bypasses hepatic first pass elimination.
- Provide a simple therapeutic regime, leading to good patient compliance that can be easily terminated by simple removal of the patch.
- Transdermal medication delivers a steady infusion of a drug over an extended period of time.
- Variability due to factors such as pH intestinal motility, food intake, etc, which make vast difference in the bioavailability of the drugs given through oral route, are not existent.
- Drugs that cause gastro intestinal upset can be good candidates for Transdermal delivery because this method avoids direct effects on stomach and intestine.

1.2. Disadvantages of TDDS[11-13]

- The transdermal route of administration is unsuitable for drugs that irritate or sensitize the skin.
- Only potent drugs are suitable candidates for transdermal delivery due to the natural limits of drug entry imposed by the skin permeability.
- Technical difficulties are associated with the adhesion of the systems to different skin types and under various environmental conditions, and the development of rate controlling conditions.
- Drugs requiring high blood levels to achieve an effect are difficult to load into a transdermal system due to large physical amount of material required.
- Another significant disadvantage of transdermal drug delivery is that skin is less permeable because it serves as protective barrier for the entry of foreign particles.
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

1.3 Basic Components of TDDS[1, 8,12,14]

Transdermal drug delivery systems are designed to support the passage of drugsubstance from the surface of skin, through its various layers, and into the systemiccirculation. There are two basic types of transdermal dosing system, those that control therate of drug delivery to the skin, and those that allow the skin to control the rate of drugabsorption.

The fundamental components of transdermal include the following.

❖ Polymer matrix

The polymers play a major role in transdermal drug delivery systems of drugs.The polymers should fulfill the following requirements.

- Molecular weight, physical characteristics, and chemical functionality of the polymer must allow the diffusion of the drug substances at desirable rate.
- The polymer should be chemically non-toxic, non reactive or it should be an inert drug carrier.
- The polymer must be easy to manufacture and fabricate into the desired product.
- It should allow incorporation of large amount of active agent.
- The polymer and its decomposed product should be nontoxic.
- The cost of the polymer should not be excessively high.

Some of the polymers used for transdermal devices are as follows.

- **Natural and semisynthetic polymers**

Carboxymethyl cellulose, cellulose acetate phthalate, ethyl cellulose, gelatin, methyl cellulose, starch, shellac, waxes natural rubber etc.

- **Synthetic elastomers**

Polybutadiene, polysiloxane, acrylonitrile, butyl rubber, Neoprene, polyisoprene, ethylene-propylene-diene-terpolymer etc.

- **Synthetic polymers**

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polystyrene polyester, polyacrylate, polymethylmethacrylate, polypropylene etc.

❖ The drug substance

The following are some of the desirable properties of a drug for transdermaldelivery.

- The drug should have molecular weight less than 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.
- The half-life of drug should be short.
- The drug must not induce a cutaneous or allergic response.
- The drugs, which degrade in gastrointestinal tract or inactivated by hepatic first pass effect are suitable candidates for transdermal drug delivery system.

❖ Penetration enhancer[15]

Penetration enhancers are molecules, which reversibly alter the barrier properties of the stratum corneum. They aid in the systemic delivery of drugs by allowing the drug to penetrate more readily to viable tissue.

1.4. Mechanism of action of permeation enhancers

❖ **Table 1.1: Different class of enhancers and their mechanism of action.[15]**

Class	Examples	Mechanism of action
Hydrating Substances	Water Occlusive preparations	Hydrates the SC
Keratolytics	Urea	Increase fluidity and hydrates the SC
Organic Solvents	Alcohols Poly ethylene glycol	Partially extracts lipids Replace bound water in the intercellular spaces Increase lipid fluidity
Fatty acids	Oleic acid	Increase fluidity of intercellular Lipids
Terpenes	Menthol	Opens up polar pathway
Surfactants	Polysorbates Sod lauryl sufate	Penetrates into skin, micellar solubilisation of SC
Azone	1-Dodecylhexahydro-2HAzepine- 2on2	Disrupts the skin lipids in both the head group and tail region

❖ **Backing membrane**

It provides protection from external factors during application period. The backing layer must be flexible and provide good bond to the drug reservoir-thereby preventing the drug from leaving the dosage form from the top and accept printing. They are usually impermeable to water vapours. The most commonly used backing materials are polyethylene terephthalate, metalized polypropylene, metallized plastic, pigmented polyester film etc

❖ **Adhesives**

An adhesive system should fulfill the following requirements.

- It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with skin.
- It should adhere to the skin aggressively.
- It should be easily removable without leaving an unwashable residue.
- It should be physically and chemically compatible with the drug, and excipients.
- It should not affect the permeation of the drug.
- The adhesive property should not deteriorate as the drug, enhancers and excipients permeate into the adhesive.

1.3. APPROACHES USED IN THE DEVELOPMENT OF TDDS.[1]

Four different approaches have been utilized to obtain transdermal drug delivery systems.

❖ **Matrix diffusion-controlled systems**

In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix (Figure 1.3). The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The drug reservoir can be formed by dissolving drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum.

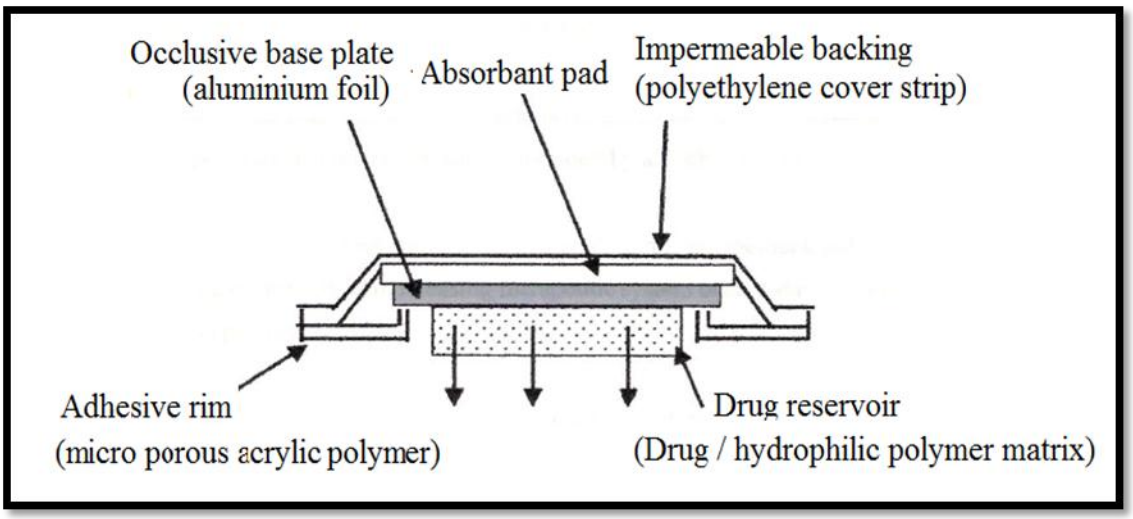

Fig. 1.2: Matrix controlled drug delivery system.

The drug reservoir containing polymer disc is then pasted on to an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing.

(Nitro-Dur and Nitro-Dur II / Key Pharmaceuticals, USA).

❖ **Membrane permeation-controlled systems**

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling membrane, which may be micro porous or non-porous (Figure 1.4). A thin layer of drug compatible, adhesive polymer like silicone or polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the transdermal system and skin surfaceThe major advantage of membrane permeation controlled transdermal system is the constant release of drug. An example is Nitroglycerin-releasing transdermal system (Transderm-Nitro/Ciba, USA) for once a day medication in angina pectoris.

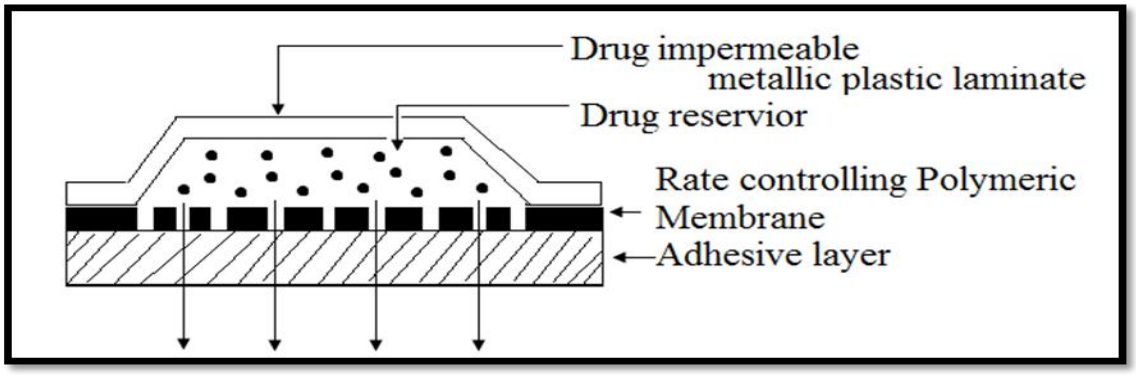

Fig. 1.3: Membrane controlled transdermal delivery system.

❖ **Adhesive dispersion-type systems**

This system is a simplified form of the membrane permeation-controlled system. Here the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer eg., poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer (Figure1.5).

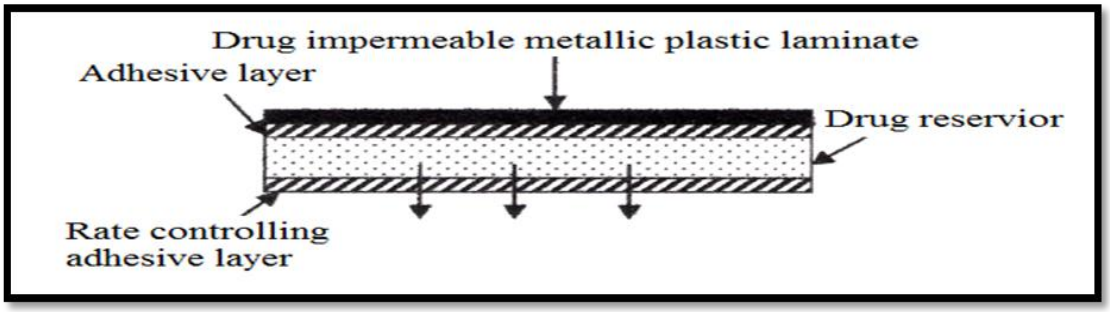

Fig.1.4: Adhesive dispersion-type transdermal drug delivery system.

On the top of the drug reservoir layer, thin layers of non-medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion controlled delivery system. Example of such delivery system is, Isosorbidedinitrate releasing transdermal therapeutic system (Frandol tape/Yamanouchi, Japan) once-a-day medication of angina pectoris.

❖ **Microreservoir type or microsealed dissolution controlled systems**

This system is a combination of the reservoir and matrix diffusion type drug delivery systems. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-soluble liquid polymer and then dispersing the drug suspension homogenously in lipophilic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs (Figure 1.6).

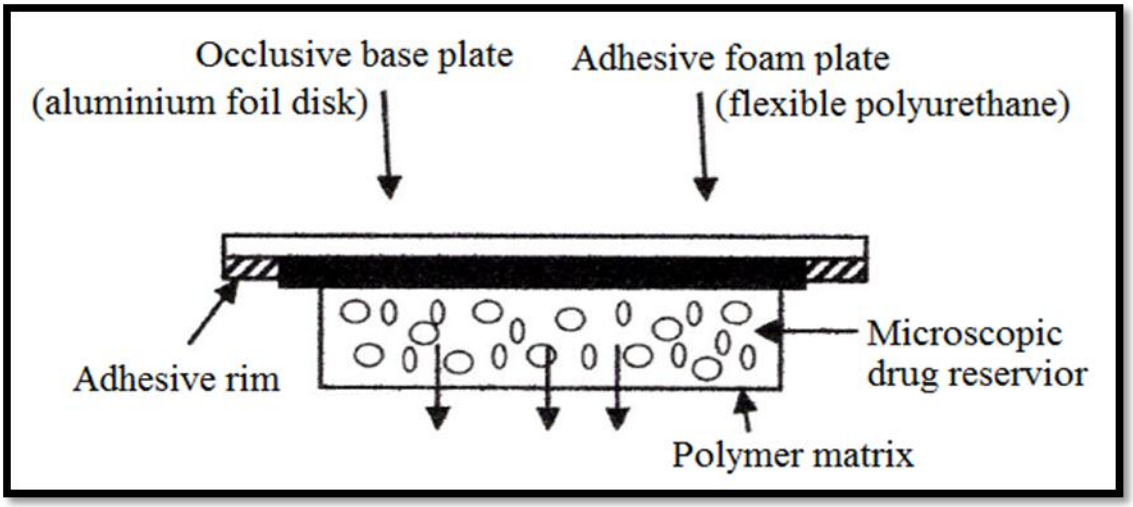

Fig. 1.5: Microreservior type transdermal drug delivery system.

The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and fixed thickness. Positioning the medicated disc at the center and surrounding it with an adhesive produce a transdermal therapeutic system. Example of such delivery system is, Nitroglycerin releasing transdermal therapeutic system (Nitro disc, Searle, USA) for once a day therapy of angina pectoris is a good example of this class.

From ancient times,Neem has been used for various therapeutic activities including its effective antimicrobial activity against various pathogenic micro-organisms as well as for it's reasonable anti-inflammatory activity. For present research work Neem extract was used to preparation of herbal medicated monolithic matrices which might exibit good antibacterial and antimicrobial activity.

1.5. PLANT PROFILE: *Azadirachta indica*,[16,17]

1	Kingdom	Plantae
2	Unranked	Angiosperm
3	Unranked	Eudicots
4	Unranked	Rosids
5	Order	Sapondales
6	Family	MAliaceae
7	Genus	Azadirchata
8	Binomial name	***Azadirachta indica*** A.Juss.,
9	Synonyms	***Antelaeaazadirachta***(L.)Adelb. ***Meliaazadirachta***L.***Melia*** Brandis

- Synonym : Margosa
- Biological source: It consist of all aerial parts of plant known as Azadirchata indica,
- family Meliaceae
- Geographical Source: It is found in Indica , Pakistan, Bangladesh, Srilanka, Thialand.
- Active constituents:

Good no. of chemicals isolated from plant belon to classess diterpenes triterpins: B- sitosterol, stigmasterol(leaf)
Limonoids: Maliantrol (seed oil) nimbidine(seed oil),Nimbendiol(seed oil) and
Azadiractin (seed).
Sulphurous compound: No. of cyclic tri and tetrasulphides (leave).
Flavanol glycosides: Nimaton, quercetin, myrecetin,kaempferol.Neem leave contain not less than 1.0%w/w of rutin.

2. MATERIAL AND METHODS

- **Materials**

2.1. List of chemicals and reagents

All the materials used in the formulations, evaluations are listed below. The chemicals used were of laboratory grade.

Table.2.1: List of chemicals and reagents.

Materials	Source
Methanol	S.D. Fine Chem. Ltd., Mumbai
Polyethylene Glycol- 400	S.D. Fine Chem. Ltd., Mumbai
Tween 80	S.D. Fine Chem. Ltd., Mumbai
Potassium dihydrogen phosphate	S.D. Fine Chem. Ltd., Mumbai
Potassium Chloride	Qualigenes fine chemicals, Mumbai
Sodium hydroxide	S.D. Fine Chem. Ltd., Mumbai
Fused Calcium Chloride	Merck Ltd., Mumbai
Sodium CMC	S.D. Fine Chem. Ltd., Mumbai
NutientAgar	Hi-media Laboratories, India
Mannitol Salt Agar	Hi-media Laboratories, India

2.2. Equipments and apparatus

Table 2.2: List of equipments and apparatus.

Equipments	Company
Electronic single pan balance	DS-852J series, Essae-Teraoka Ltd
Hot air oven	Techno scientific products
Sonicator	CD-4820 Techno scientific pdts
Incubator	Techno scientific products
UV-Visible spectrophotometer	Shimadzu UV-1800pc, Japan
Digital ultrasonic cleaner	Techno scientific products
Teflon Plates	Fabricated locally
FT-IR spectrometer (4000/6000Series)	IR affinity-1, Shimadzu, Japan.

2.3.Preparation of Neem Extracts

The fresh leaves of *Azadirchata indica* (Neem) were collected from Botanical Garden of Willingdon college, Sangli. Leaves were dried under shade by spreading in thin layer aluminum trays for 10-15 days. Leaves were turned upside down repeatedly during the process of drying to achieve complete drying. The dried leaves of *Azadirchata indica* (Neem) were powdered using electric grinder and sieved through a 40 mesh screen.

2.4. Soxhlet Extraction[18]

A ground sample of *Azadirchata indica* (Neem) leaves (40g) was placed in a "thimble" made of filter paper and placed in the soxhlet extractor. A flask containing 400 ml of the methanol was attached at the bottom and heated until extraction. The extract so obtained is concentrated by slow evaporation in a hot air oven.

2.5. Procedure for formulation of Transdermal Patch :

A dispersion type transdermal matrices were prepared using Sodium CMC as matrix forming polymer, PEG-400 as a plasticizer & a hydro-alcoholic solvent system(i.e. Methanol: Water). Tween 80 is added to polymeric solutionas a permeation enhancer for the transdermal deliveryas well as to enhance dispersion of neem extract. Here three different concentrations of Sodium CMC viz, 2%, 3% & 4% were employed for development of transdermal matrices.

Table no.2.3: Transdermal Patch.

Sr.No.	Ingridient	F-1	F-2	F-3
1	Neem Extract	100mg	100mg	100mg
2	Sodium CMC	2%	3%	4%
3	PEG-400	0.6ml	0.6ml	0.6ml
4	Water: Methanol (1:1)	10ml	10ml	10ml
5	Tween-80	q.s	q.s	q.s

- **Chracterization of Medicated Transdermal matrices.**

2.6. Physical appearance: The prepared patches were physically examined for uniformity of colour, clarity and surface texture.

2.7.Thickness uniformity

The thickness of patches was measured by using electronic caliper, with a least count of 0.01 mm. Thickness was measured at three different points on the film and average readings were taken.

2.8.Uniformity of weight

The patch of size 1x1 $cm^2$was cut and weight of each patch was taken individually, the average weight of the patch was calculated.

2.9.Tensile strength:

Tensile strength of the patches was determined with Modified tensile strength apparatus (Fig No.1.8). Here thedirect measurement of tensile load at break of the films was done. The test apparatus comprised of two arms for holding the patch vertically, the upper arm is fixed which holds the patch, the patch hangs freely from the upper arm & is attached to the lower arm which can be applied with load. The load is applied gradually till the patch breaks thus determining the tensile load at the breaking point. Tensile strength is determined in kg directly.

Fig No2.1:. Modified Tensile Strength Apparatus.

2.10. Folding endurance

The folding endurance was measured manually for the prepared patches. A strip of patch (2 x 2 $cm^{2)}$ was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

2.11.Percentage moisture loss

The patches were weighed individually and kept in a desiccator containing calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

$$\%\ \text{moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100$$

2.12.Percentage moisture uptake

The patches were weighed accurately and placed in a desiccator where a humidity condition of 80-90 % RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

$$\%\ \text{moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} * 100$$

2.13.Water vapor transmission (WVT) rate

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 80-90 % RH. The cells were taken out and weighed after 24 hrs. The amount and rate of water vapor transmitted was calculated by the difference in weight using the formula.

$$\text{Water vapour transmission rate} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Time} * \text{Area}}$$

Water vapour transmission rate is usually expressed as the number of grams of moisture gained/hr/cm^2

2.14.Assessment of *in-vitro* Antibacterial activity of patches[19]

The antimicrobial efficacy of prepared patches is evaluated by modified agar diffusion method, here the transdermal matrices of 1 cm^2 were cut and directly placed over agar surface previously seeded with 24hr old broth culture (Mcfarland Standard 0.5) of S. aureus for the diffusion of antibacterial principle. Blank patches without antibacterial extracts served as a control. Finally all the plates were incubated at 37^0C for 24 hours & the zones of inhibitions obtained were recorded.

2.15.Assessment of *in-vitro* anti-inflammatory *activity*[20,21]

For assessment of *in-vitro* anti-inflammatory activity, method of Mizushima et al., was employed & the Inhibition of albumin denaturation was recorded. Here the original method was slightly modified. The reaction mixture was consisting of test extract and 1% aqeuous solution of albumin fraction. The sample was incubated at37^0C for 20 minutes then heated at 57^0C for 20 minutes. After cooling the sample, the turbidity was measured spectrophotometrically at 660 nm. The experiment was performed in triplicate. Percent inhibition of protein denaturation was calculated as follows:

Percentage inhibition = $(Abs_{control}–Abs_{sample})*100/ Abs_{control}$

3. RESULTS

3.1. Thickness

Table 3.1: Thickness uniformity data of Herbal medicated monolithic matrices.

Formulation Code	Trial 1 mm	Trial 2 Mm	Trial 3 Mm	Mean ± S.D* Mm
F-1	0.18	0.18	0.19	0.200 ± 0.020
F-2	0.19	0.21	0.21	0.203 ± 0.011
F-3	**0.19**	**0.21**	**0.20**	**0.2**

3.2. Weight Uniformity

Table 3.2: Weight uniformity data of Herbal medicated monolithic matrices.

Formulation code	Trial 1	Trial 2	Trial 3	Mean ± S.D.* (gm)
F-1	0.04	0.03	0.03	0.033± 0.005774
F-2	0.04	0.05	0.04	0.0336 ± 0.005774
F-3	0.05	0.06.	0.05	0.0533±0.0057

3.3. Tensile strength

Table 3.3: Tensile strength data Herbal medicated monolithic matrices.

Formulation Code	Trial 1	Trial 2	Trial 3	Mean ± S.D.* (gm)
F-1	270	275	270	271.66±2.886
F-2	290	285	290	286.66±2.886
F-3	310	305	310	308.33±2.886

3.4. Folding endurance

Table 3.4: Folding endurance data of Herbal medicated monolithic matrices.

Formulation Code	Trial 1	Trial 2	Trial 3	Mean ± S.D.*
F-1	80	79	79	79.33± 0.54
F-2	81	82	83	82± 1
F-3	82	83	84	83

3.5.Percentage moisture absorption

Table 3.5: Percentage moisture absorption data of Herbal medicated monolithic matrices.

Formulation Code	Trial 1	Trial 2	Trial 3	Mean ± S.D.* (%)
F-1	67.22	67.45	68	67.55
F-2	67.11	67.15	67.89	67.38
F-3	66.66	65.66	66.66	66.32

3.6. Percentage moisture loss

Table 3.6: Percentage moisture loss data of Herbal medicated monolithic matrices.

Formulation Code	Trial 1	Trial 2	Trial 3	Mean ± S.D.* (%)
F-1	67.11	67.15	67.89	67.38
F-2	67.11	67.15	67.89	67.38
F-3	66.66	65.66	66.66	66.32

3.7.Water vapour transmission rate

Table 3.7: Water vapour transmission data of prepared matrices.

Formulation Code	Trial 1	Trial 2	Trial 3	Mean ± S.D.* (gm $cm^{-2}h^{-1}$)
F-1	0.58	0.58.	0.57	0.57±0.05
F-2	0.55	0.56	0.57	0.56±0.01
F-3	0.52	0.5	0.5	0.50±0.01

3.8.In vitro anti-inflammatory activity

Table 3.8: % inhibition of albumin denaturation data of prepared patches.

Sr.No.	Formulation	% Inhibition of albumin denaturation
1	F-1	35.45
2	F-2	35.24
3	F-3	35.40

4. DISCUSSION

4.1. Physical appearance

The patches formed were yellow in color, semi-transparent/translucent in appearance.

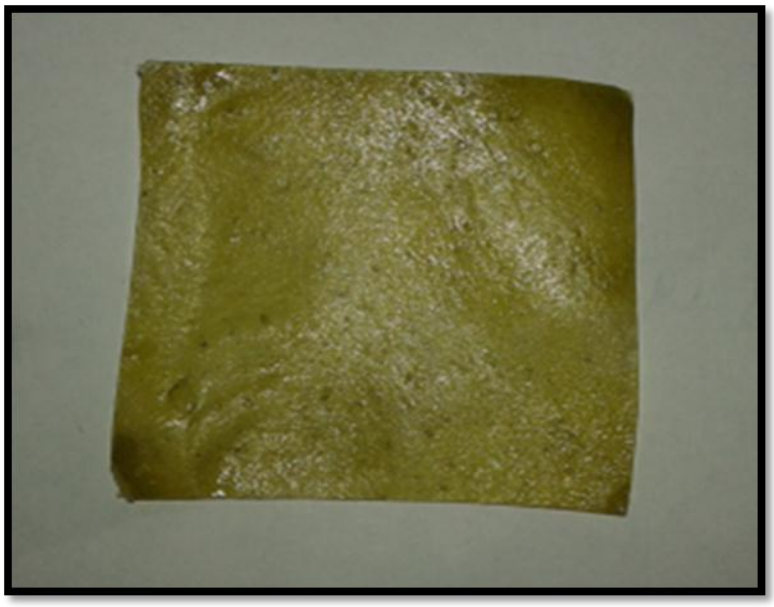

Fig No. 4.1.: Showing characteristic texture of the TDDS & have a characteristic texture.

4.2.Thickness

With the help of Digital calipers, the thickness of patches was measured and the average thickness was noted. The thickness results are given in Table 1.5 The result indicates that there was no much difference in the thickness within the formulations. The order of the thickness of patches is F-3 > F-2> F-1.

4.3.Weight uniformity

Drug loaded patches (1 x 1 cm^2) were tested for uniformity of weight and the results of weight uniformity are given in Table 1.6. Lesser S.D. values indicate that the patches a uniform. Thisis in agreement with the uniformity of the thickness.

4.4Tensile strength

Tensile strength of the patches was determined with Modified tensile strength apparatus (Fig No.). Here the

direct measurement of tensile load at break of the films was done. The results (average of 3 determinations) are given in the Table 1.7. The order of tensile strength of the patches is F-3> F-2 > F-1. With increase in CMC concentration the tensile strength of patches was increased.

4.5.Folding endurance

The recorded folding endurance of the patches was shown in Table 1.8. It depicits all formulations have good film properties. The folding endurance of the patches are in the following order F-3> F-2 > F-1. The results indicate, as the CMC concentration increases the folding endurance of the patches increases.

4.6.Percentage moisture absorption

The recorded Percentage moisture absorption of the patches was shown in Table.

1.9. The percentage moisture absorption of the prepared patches is in following orderF-1>F-2>F-3. The results show the moisture absorption of all the patches are within the acceptable limit.

4.7.Percentage moisture loss

The recorded Percentage moisture loss of the patches was shown in Table 2.0. The percentage moisture absorption of the prepared patches is in following order F-1>F-2>F-3.

4.8. Water vapour transmission rate (WVTR)

The water vapour transmission rates of different formulations were evaluated and the results are shown in table 2.1. The WVTR was in the following order F-1>F-2>F-3.

4.9.Assessment of *in-vitro* anti-inflammatory activity

All the formulations were evaluated for anti-inflammatory activity by noting the % of inhibition of albumin denaturation. There were no significant differences in the % inhibition values obtained for the prepared formulations.

4.10.Assessment of *in-vitro* antibacterial activity

All the test patch formulations containing the antibacterial extract showed significant antibacterial activity, the zones of inhibitions obtained for the all three formulations are nearly same. While control patches without drug showed no zones of inhibition at all.

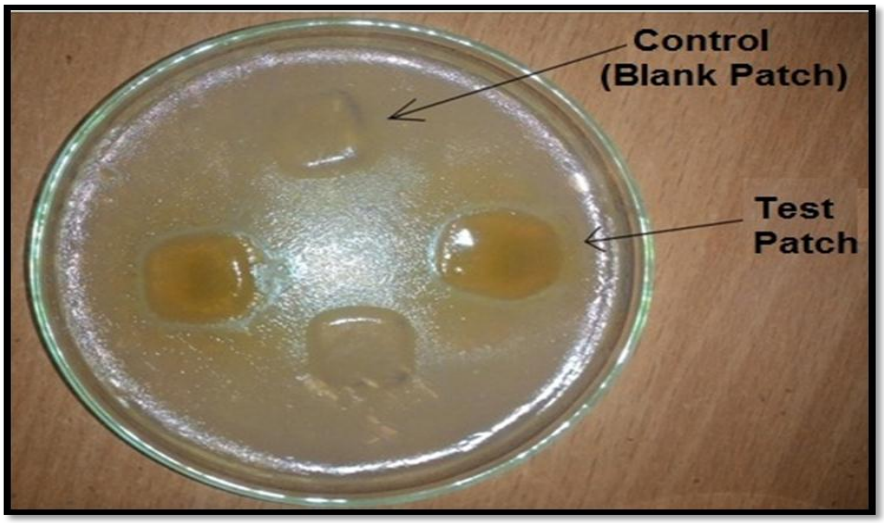

Fig. No. 4.1: Test patches with zones of inhibition.

5. CONCLUSION

Anti-bacterial & anti-inflammatory potential of Neem is well known & Indians had been using it from ancient times. In this research work the methanolic extracts of neem were used as a crude drug for the development of the medicated monolithic matrices using solvent evaporation technique. The prepared patches were subjected for evaluation parameters such as physical appearance, weight variation, thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss, water vapor transmission rate, tensile strength, in-vitro antibacterial activity & in vitro anti-inflammatory activity.

All patch formulations showed good physical properties with uniform color, texture and thickness. It was found that as concentration of Sod. CMC increases the tensile strength and folding endurance of patches also increase. The tensile strengths & folding endurance of the prepared patches were found in the order F-3>F-2>F-1.

% moisture uptake & % moisture loss values of all the patches were under limit & it was found that % moisture loss as well as % moisture uptake values decrease with increasing concentration of Sod. CMC. Water vapor permeation rate also decreases with increase in concentration of sod. CMC. The water vapor permeation

rate values of the prepared patches were found to be in the order F-1>F-2>F-3.

All the formulations F-1, F-2& F3 showed the significant antibacterial & anti-inflammatory activity. From above results we can conclude that, the present research work was successful attempt for satisfactory utilization of crude herbal principle for the development of effective transdermal drug delivery system still it is a preliminary research work &Further detailed investigations and elaborate in-vivo studies need to be carried out and an in vitro – in vivo correlation need to be established to guarantee the efficiency and bioavailability of the formulation. Further studies on improving bioavailability have to be carried out with different polymers.

6. REFERENCES

1. Chein YW. 'Novel Drug Delivery Systems'. 2nd ed. New York: Marcel Dekker, 1992; 1-2, 301-50.
2. Tyle P. 'Drug Delivery Devices. Fundamentals and Applications'. New York: Marcel Dekker, 1998; 385-417.
3. Desai BG, Annamalai AR, Divya B, Dinesh BM. 'Effect of enhancers on permeation kinetics of captopril for transdermal system'. Asian J Pharm, 2008; 2: 35-7.
4. Ryan DG and Peterson TA. 4 'Myths about transdermal drug delivery. Drug Del Tech', 2003; 3(4): 1-7.
5. Pathan IB, Setty CM. 'Chemical penetration enhancers for transdermal drug delivery systems'. Trop J Pharm Res, 2009; 8(2): 173-9.
6. Benson HAE.,' Transdermal drug delivery: Penetration enhancement techniques'. Curr Drug Deliv, 2005; 2: 23-33.
7. Jain NK. 'Advances in controlled and novel drug delivery'.1st ed. Delhi: CBS Publishers, 2001; 426-48.
8. Rao YM ,Gannu R, Vishnu YV and Kishan V. 'Development of nitrendipine transdermal patches for *in vitro* and *ex vivo* characterization'. Curr Drug Deliv, 2007; 4: 69-76.
9. Mao Z, Zhan X, Tang G, Chen S. 'A new copolymer membrane controlling clonidine linear release in a transdermal drug delivery system'. Int J Pharm, 2006; 332: 1-5.
10. Aqil M, Sultana Y, Ali A. 'Matrix type transdermal drug delivery systems of metoprolol tartrate: *In vitro* characterization'. Acta Pharm, 2003; 53: 119-25.
11. Vyas SP, Khar RK. 'Controlled drug delivery concepts and advances'. 1st ed. New Delhi: Vallabh Prakashan, 2002; 411-47.
12. Tiwary AK, Sapra B and Jain S. 'Innovations in transdermal drug delivery: formulations and techniques. Recent Patents on Drug Delivery & Formulation', 2007; 1: 23-36.
13. Murthy SN, Hiremath. 'Transdermal Drug Delivery systems. In: Hiremath SRR, editor. Text book of industrial pharmacy'. India: Orient longman private limited, 2008; 27-49.
14. Singh BS and Kumar CP. 'Penetration enhancers for transdermal drug delivery of systemic agents'. J Pharm Res, 2007; 6(2): 44-50.
15. Ren C, Fang L, li T, Wang M, Zhao L, He Z. 'Effect of permeation enhancers and organic acids on the skin permeation of indapamide'. Int J Pharm, 2008; 350: 43-7.
16. Maragathavalli, S., 2Brindha, S., 3Kaviyarasi, N.S., 4B. Annadurai, B. & 5Gangwar, S.K, 'Antimicrobial Activity In Leaf Extract Of Neem(*Azadirachta Indica* Linn'., Issn 2229 – 6441, I.J.S.N., 2012; 3(1): 110-113.
17. Imam Hashmat1*, Hussain Azad2 and Ajij Ahmed, Neem (*Azadirachta indica* A. Juss) – 'A Nature's Drugstore: An overview, International Research Journal of Biological Sciences', ISSN2278-3202Vol, October 2012; 1(6): 76-79.
18. Gabriela Esparza-Díaz, Juan A. Villanueva-Jiménez*, José Lópezcollado and Daniel A. Rodríguez-Lagunes1, 'Azadirachtin Extraction Using Cold Press and Soxhlet Methods', *Biopestic. Int*, 2010; 6(1): 45–51.
19. .Orhue P. O., 2Momoh A. R. M., 1Igumbor E. O. and 1Esumeh F. I. , 'Antibacterial effect of *Azadirachta indica' (CN: Neem or Dongo Yaro)* parts onsome urinary tract bacterial isolates , Pelagia Research Library, Asian Journal of Plant Science and Research, 2014; 4(2): 64-67.
20. Damodar Reddy C*,Raja Ratna Reddy Y, Krishna Kumari C, Lokanatha O, Mamatha S, 'Antimicrobial activity of *Azadirachta Indica* (neem) leaf, bark and seed extracts',ijrpp, Raja Ratna Reddy et al., (2013) Int. J. Res. Phytochem. Pharmacol, 3(1): 1-421.