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Formulation and Evaluation of Naproxen Sodium Transdermal Patch Using Natural Polymers

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Keywords: Naproxen sodium, gelatine, jackfruit mucilage, sustains release, solvent casting method.

ABSTRACT

Naproxen sodium is a widely prescribed NSAID and used as a first-line therapy for treatment of rheumatoid arthritis, osteoarthritis, and ankylosis spondylitis. Naproxen sodium belongs to BCS class 2 and being an NSAID has major side effects such as low blood pressure, slows cardiac rhythm, anemia, bronchospasm, chronic heart failure and gastric irritation. Naproxen sodium may increase the risk of fatal heart attack, especially when it is used for long-term hence formulating such drug into transdermal drug delivery using different polymers may increase the sustain release action and reduce the side effects. The Present study includes formulation and evaluations of naproxen sodium transdermal patch using jackfruit mucilage and gelatine as polymers, natural polymers are used as they are cost-effective and have fewer side effects when compared to synthetic polymers. The transdermal patches with both the polymers using solvent casting method (F1 to F9) were prepared & evaluated for various parameters like thickness, moisture content, moisture uptake, drug content, flatness, *in vitro* drug release, weight uniformity, folding endurance. The naproxen patch prepared using gelatine, f8 formulation was optimized as well as naproxen patches prepared using jackfruit mucilage, f8 formulation was optimized. The formulation containing gelatine showed greater release following first-order kinetics with non-fickian diffusion mechanism when compared to patches prepared using jackfruit mucilage.

INTRODUCTION:

Now about two third of drugs are taken orally, but these are not as effective as required. To improve upon the difficulties transdermal drug delivery system has emerged. Amongst all techniques which are used for releasing the drugs in a controlled way, transdermal drug delivery system (TDDS) is recognized as one of the most reliable and effective technique. Delivery of drugs through the skin has been an attractive as well as a challenging area for research.[1]Maintenance of drug level above minimum effective concentration has always been considered as a superior mode of drug delivery. Limitation of first-pass metabolism and also to maintain constant, prolonged, and effective drug concentration levels in the plasma is possible through transdermal drug delivery system.[2]

Advantages of transdermal drug delivery: [(3-8)]

1. By TDDS gastrointestinal drug absorption difficulties can be avoided covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other oral administration drug.

2. Improves the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastric irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.

3. Longer duration of action results in a reduced dose frequency.

4. Avoids the inconvenience of parenteral therapy.

5. The self administration is possible.

6. Maintains the plasma concentration of potent drug.

7. Provides extended therapy with a single application.

8. Easy elimination of drug delivery is possible in case of toxicity.

Disadvantages: [(9-12)]

1. Drugs with very low or high partition coefficient fail to reach blood circulation.

2. Only potent drugs are suitable for transdermal patch because of the limits of drug entry into the skin.

3. The barrier function of the skin may changes from one site to another on the same person, from person to person and with age**.**

4. If the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.

MATERIALS AND METHODS:

MATERIALS:

Naproxen sodium, gelatine, glycerine, dimethyl sulphoxide, acetone (SD FINE Chem. Limited, Mumbai), jackfruit mucilage

METHODS:

PREPARATION OF NAPROXEN SODIUM TRANSDERMAL PATCH BY SOLVENT CASTING METHOD USING GELATIN

Transdermal patches of different ratios from F1-F9 was prepared by solvent casting method in a glass mold of 25cm^2**.**The casting solutions were prepared by sprinkling weighed amount of gelatine in 10 ml of distilled water and was kept aside for 15 minutes then measured amount of glycerine was added and heated to 60^{0}c until gelatine dissolves. Then dug of weighed quantity was added and solution was then transferred to mold after cooling and controlled solvent evaporation was achieved by placing an inverted funnel over the mold. It was left undisturbed at room temperature for one day.

Table 1: Formulation composition of transdermal patch

Formulation code	Gelatine (w/v)	Glycerine (w/w)	Distilled water (ml)
F1	0.5	2	10
F2	1	2	10
F3	2	2	10
F4	3	2	10
F5	4	2	10
F6	2	0.5	10
F7	2	1	10
F8	2	3	10
F9	2	4	10

PREPARATION OF NAPROXEN SODIUM TRANSDERMAL PATCH BY SOLVENT CASTING METHOD USING JACKFRUIT

Characterization of Jackfruit mucilage

Table 2: Characterization of Jackfruit mucilage

Characterization of Jackfruit mucilage	values
pH	6
Swelling index	2 ml
Viscosity	1704 cps

EXTRACTION OF MUCILAGE:

Jackfruit mucilage was extracted by maceration process .the ripe fruit pulp of Artocarpus heterophyllus was separated and the seeds were removed and the pump was soaked in distilled water with occasional shaking. The soaked pulp was ground in grinder and was kept for 24hrs. Material was squeezed through Muslim cloth to separate Marc from filtrate. The filtrate was precipitated with organic solvent (acetone) and mucilage was stored in fridge.

Figure 1: Jackfruit soaked in distilled water

Preparation of patch:

Transdermal patches of different ratios from f1-f9 were prepared by solvent casting method in a glass mold of 25cm^2. The casting solutions were prepared by taking weighed amount of jackfruit mucilage in10 ml of distilled water and was kept aside for 15 minutes then measured amount of glycerine was added, DMSO was added as penetration enhancer along with a weighed quantity of drug. The solution was then transferred to mold and Controlled solvent evaporation was achieved by placing an inverted funnel over the mold. It was left undisturbed at room temperature for one day.

Table 3: Formulation composition of transdermal patch

Formulation code	Jackfruit (w/v)	Glycerine (w/w)	Penetration enhancer (ml)	Distilled water(ml)
F1	0.5	0.5	0.5	10
F2	1	1	0.5	10
F3	2	1	0.5	10
F4	3	1	0.5	10
F5	4	1	0.5	10
F6	2	1	0.5	10
F7	2	0.5	0.5	10
F8	2	0.6	0.5	10
F9	2	0.7	0.5	10

EVALUATION

1. Thickness of the Patch: The thickness of the drug-loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.[13]

2. Percentage Moisture Uptake: The weighed films are to be kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below-mentioned formula[14]

Percentage moisture uptake = [Final weight-Initial weight/Initial weight] × 100.

3. Moisture Loss: The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40^{o}C. After 24 hrs the films are to be reweighed and determine the percentage of moisture loss from the below formula[15]

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

4. Folding Endurance: A strip of specific area is to be cut evenly 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 the folding endurance

5. Flatness Test: Three longitudinal strips are to be cut from each film at different portion like one from the center, another one from the left side and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity

in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.[16]

Flatness = $[L_1-L_2 / L_1] \times 100$ Where L_1 is the final length of each strip and L_2 is the initial length of each strip.

6. Weight uniformity

The patches are dried at 60°C before weighing. The weight uniformity of the patch is measured by cutting and weighing the 1 cm^2piece of 3 patches and then calculating the weight variation. The mean of the 3 is taken as the weight of the patch. The individual weight should not deviate significantly from average weight.[17]

7. Weight Variation: The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation [18]

8. Drug content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. *In vitro* permeation studies:

Patches were subjected to an *in-vitro* permeation studies by using Franz diffusion cell containing cellophane membrane. The patches were placed in a donor compartment over the membrane and covered with clips. The temperature of the receptor compartment was maintained at 37±2ºC throughout the experiment. The compartment was in contact with the ambient environment. The amount the drug permeated through membrane was determined by withdrawing 1ml of sample at predetermined time interval and replacing them with an equal volume of buffer. The withdrawal samples filtered and the samples were analyzed spectrophotometrically

10. Permeation flux (J):

Flux is defined as the amount of material flowing through a unit cross-sectional barrier in a unit time.[19]

It is calculated by: Flux (J) = P x CD

Where CD = concentration of drug in donor solution, P = permeability coefficient.

11. Permeability coefficient: The velocity of drug passage through the membrane/skin in mcg/cm2/hour[20.] The permeability coefficient was calculated from the slope of the graph of percentage of drug transported vs. time as:

P = slope x Vd/S (1)

Where Vd = volume of donor solution,

S = surface area of tissue.

12. RELEASE RATE: It is the slope of the Higuchi plot and the units are ($\mu g/cm^2/hr^{-1/2}$)

13. TRANSDERMAL DOSE = (Bioavailability ×Total dose)/ 100

RESULTS AND DISCUSSION:

Analytical method development for estimation of naproxen sodium:

An ultraviolet spectrophotometric method based on measurement of absorbance at 270nm in buffer of P^H 7.4 was used for the estimation of naproxen sodium. The method was validated for linearity(r=0.99) and precision (%C.V<1%).

Table 4: Standard graph of naproxen sodium

Concentration (µg/ml)	Absorbance (n=3) (X±s.d)	% C.V
2	0.039	0.066
4	0.082	0.029
6	0.122	0.043
8	0.162	0.013
10	0.198	0.05
12	0.243	0.01

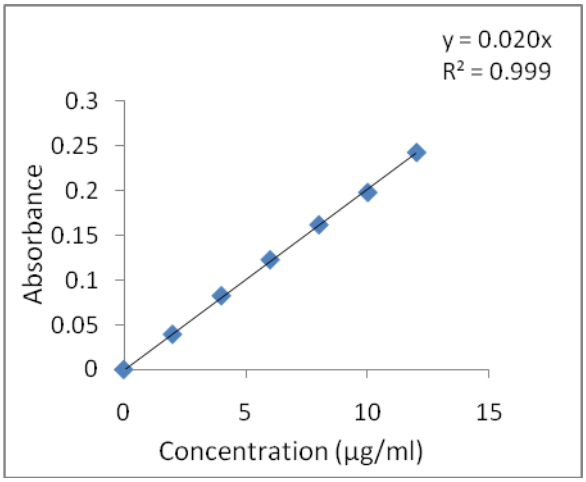

Figure 2: Standard curve of Naproxen sodium.

FTIR Spectra of Naproxen Sodium and various Excipients:

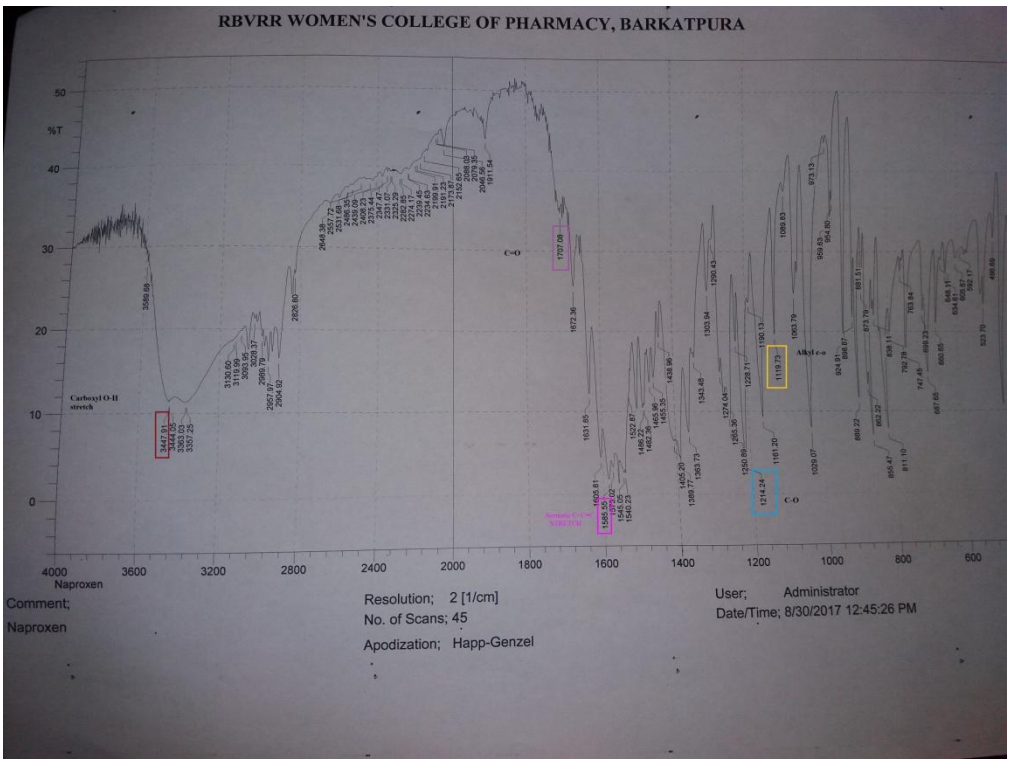

Figure 3: FTIR spectra of pure drug (Naproxen Sodium)

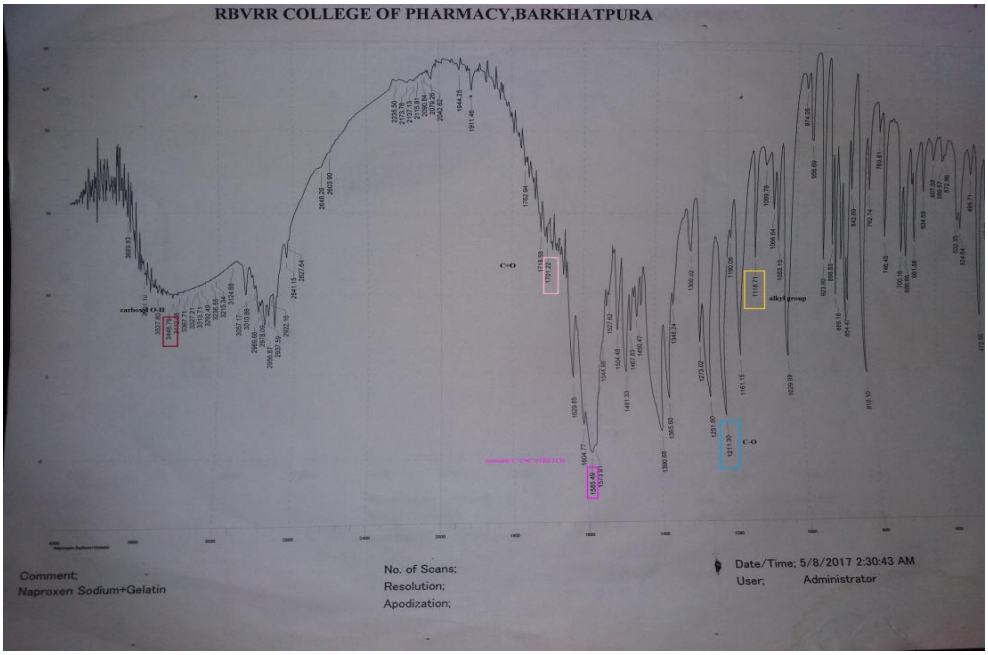

Figure 4: FTIR spectra of drug and polymer (gelatin)

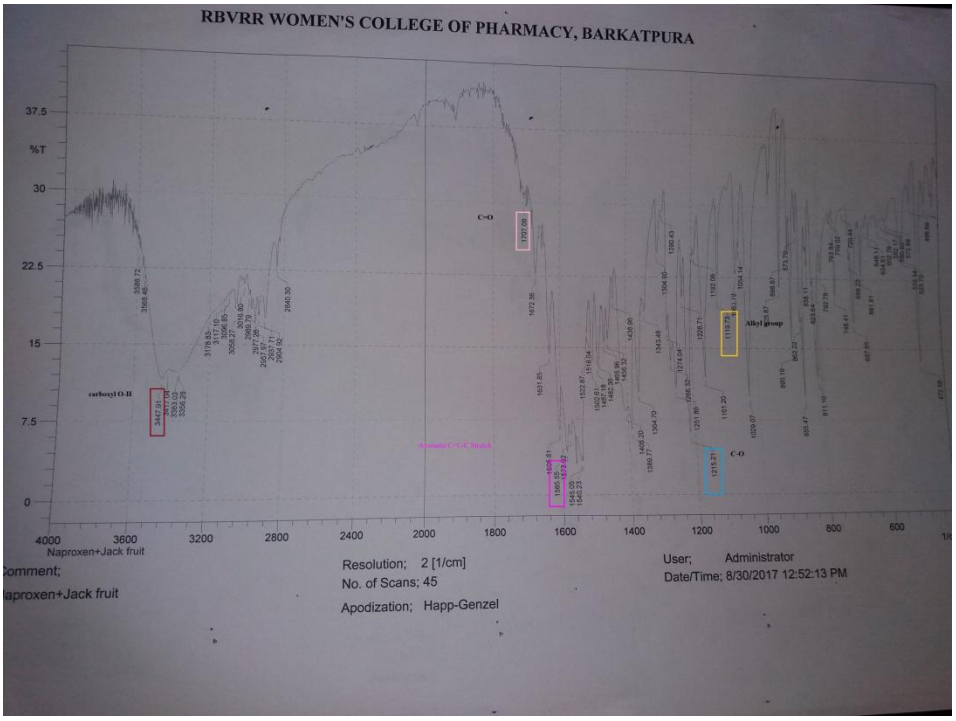

Figure 5: FTIR spectra of drug and polymer (jackfruit mucilage)

Drug-excipient compatibility was evaluated using FTIR spectra:

In FTIR spectra aromatic C=O stretching vibrations at 1730-1700 cm^{-1}.Aromatic groupC=C-C Stretch at1615-1580 cm^{-1}.O-H stretch at 3500-2400 cm^{-1}.C-O stretching vibrations at 1320-

1210 cm^{-1}. The Ethyl groupAryl-O- stretching vibrations at 1270-1230 cm^{-1}. Alkyl-C- stretching vibrations at1150-1050 cm^{-1}.

It was observed that there is no chemical interactions and functional alteration between the drug and excipient

Table 5: Evaluation of naproxen sodium TDDS patch containing gelatin

CODE	Thickness	Drug content(mg)	Cum %DR	flatness	Folding endurance	Moisture content	Moisture uptake
F1	0.1	8.4	85.3	96	312.3	2.33	3.7
F2	0.1	8.1	82.5	98	327.6	7.86	3.1
F3	0.11	7.8	77.2	100	300	1.12	2.32
F4	0.16	7.1	72.2	90	280	2.66	5.1
F5	0.28	5.0	51.6	100	211	3.53	4.16
F6	0.1	6.1	62	100	287.3	10.6	7
F7	0.1	6.6	66.4	100	255.3	1.8	8
F8	0.12	9.2	93.5	100	299.6	0.73	1.05
F9	0.17	9.6	96.6	100	313.6	1.75	7.4

Values in parenthesis are expressed as X±S.D (n=3)

Table 6: Evaluation of naproxen sodium TDDS patch containing jackfruit mucilage

CODE	Thickness	Drug content(mg)	Cum %DR	flatness	Folding endurance	Moisture content	Moisture uptake
F1	0.1	9.1	92.1	90	230	3.63	9.18
F2	0.1	9	91.1	96	219	0.99	7.08
F3	0.1	7.6	77.6	94	278	1.54	1.24
F4	0.186	8.5	85	100	96	1.07	1.19
F5	0.196	6.4	64.9	99	86	0.723	0.95
F6	0.2	8.6	86.7	98	287	1.42	0.96
F7	0.3	5.9	59.8	97	320	4.05	3.26
F8	0.296	8.7	88	98	297	1.22	0.6
F9	0.313	8.9	89.6	100	210	0.723	0.55

Values in parenthesis are expressed as X±S.D (n=3)

Table 7: permeation flux and permeability coefficient of drug through optimized formulations

Formulation code	**Flux (**µg/cm^2/hr)	**Permeability coefficient** (cm/hr)
F8 Naproxen patch (gelatin)	0.249	0.035
F8 Naproxen patch (jack fruit mucilage)	1.270	0.272

RELEASE RATE: The release rate was found to be 19.5 µg/cm^2/hr$^{-1/2}$ for optimized formulation prepared using gelatin.

And for the optimized formulation prepared using jackfruit mucilage the release rate was 18.1µg/cm^2/hr$^{-1/2}$

TRANSDERMAL DOSE: the transdermal dose is 9.5mg daily.

Fig 6: Zero order plot for optimized F8 formulation of naproxen patch containing gelatin

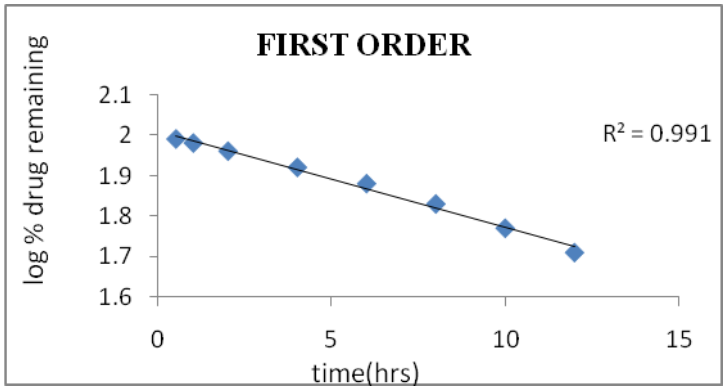

Fig 7: First order plot for optimized F8 formulation of naproxen patch containing gelatin

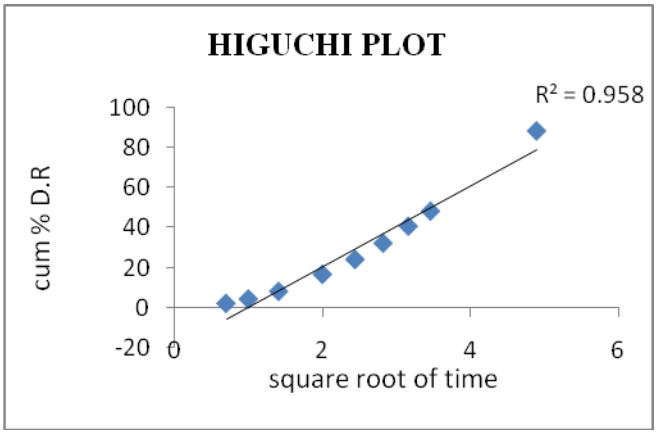

Fig 8: Higuchi plot for optimized F8 formulation of naproxen patch containing gelatin

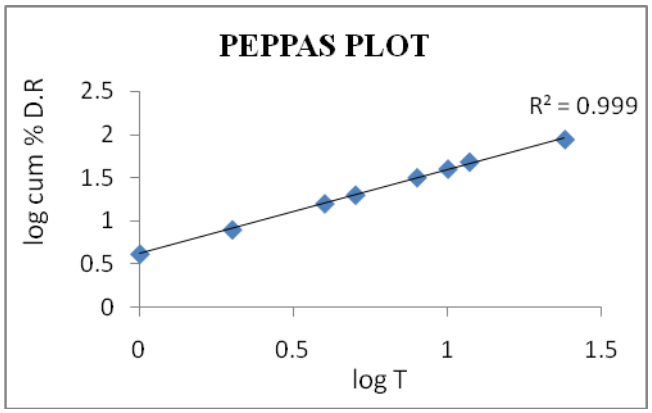

Fig 9: Peppas plot for optimized F8 formulation of naproxen patch containing gelatin

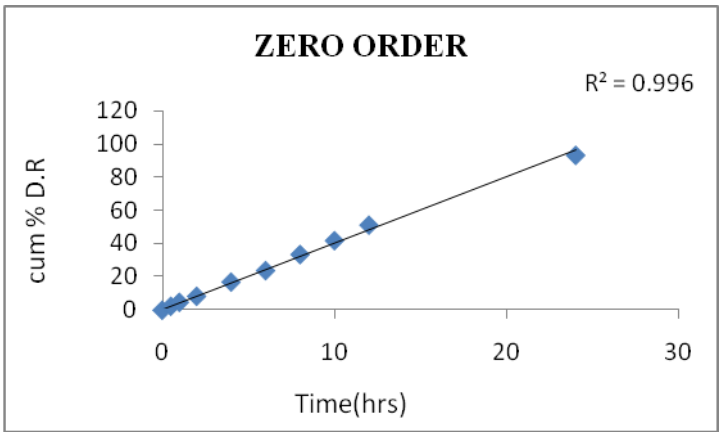

Fig 10: Zero order plot for optimized F8 formulation of naproxen patch containing jackfruit mucilage

Fig 11: First order plot for optimized F8 formulation of naproxen patch containing jackfruit mucilage

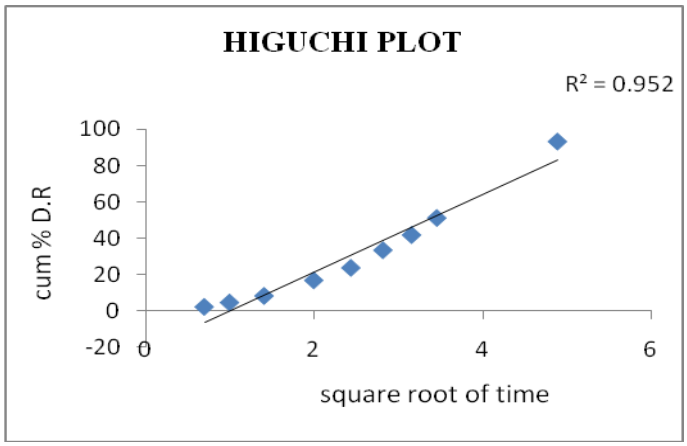

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Fig 12: Higuchi plot for optimized F8 formulation of naproxen patch containing jackfruit mucilage

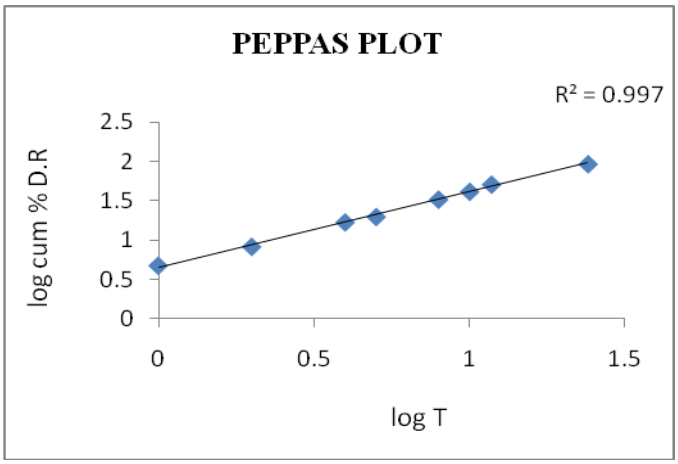

Fig 13: Peppas plot for optimized F8 formulation of naproxen patch containing jackfruit mucilage

Table 8: Kinetic Parameters for Formulations prepared by using Gelatin and jackfruit mucilage

Formulation code	Zero-order plot (R^2)	First order plot (R^2)	Higuchi plot(R^2)	Peppas plot(R^2)
F8 formulation containing gelatin	0.995	0.991	0.958	0.999
F8 formulation containing jackfruit mucilage	0.996	0.912	0.952	0.997

From the results, it was observed that the formulations followed first order release with non-fickian diffusion mechanism.

Comparison of the optimized formulation with the marketed product

Table 9 Comparison of the optimized formulation with the marketed product

Formulations	Drug Content (%)	Releases Drug up to (hours)
Naproxen patch with gelatin	92	24
Naproxen patch with jackfruit mucilage	87	24
Xenobid gel (marketed formulation	81	10

When the optimized formulations were compared with the marketed Xenobid gel the drug content of the gel was found to be 81% with drug release up to 10 hours which was less when compared to prepared formulations. The naproxen sodium transdermal patches prepared with natural polymers sustained the drug release up to 24 hours with maximum drug content.

DISCUSSION

❖ Transdermal patches of Naproxen sodium using natural polymers were prepared by solvent casting technique at different ratios (F1-F9) to get a desired sustain release of the drug. Altogether 18 formulations were prepared (9 formulations using gelatin as polymer and the other 9 using jackfruit mucilage). The patches prepared was evaluated for parameters like thickness, flatness, moisture content, moisture uptake, weight variation, folding endurance, drug content. The viscosity of the jackfruit mucilage was found to be 1704cps with pH 6 and

swelling index 2 ml respectively and hence jackfruit mucilage can be a suitable polymer in patch formation.

❖ The Thickness of the optimized formulation prepared using gelatin and jackfruit mucilage was found to be 0.12mm and 0.296mm.

❖ The Moisture content of the optimized formulation prepared using gelatin and jackfruit mucilage was found to be 0.73% and 1.22%.

❖ The Moisture uptake of the optimized formulation prepared using gelatin and jackfruit mucilage was found to be 1.05% and 0.6%.

❖ The weight variation of the optimized formulation prepared using gelatin and jackfruit mucilage was found to be 3.45gm and 3.79gm

❖ The drug content variation of the optimized formulation prepared using gelatin and jackfruit mucilage was found to be 9.2mg and 8.7 mg

❖ The flux (J) through cellophane membrane of optimized f8 formulation (gelatin) was found to be 0.249µg/ml/cm^2 and the flux (J) of f8 formulation using jackfruit mucilage was 1.270µg/ml/cm^2.The permeability coefficient (P) of naproxen patch using gelatin and jackfruit mucilage are 0.035 and 0.272 and the permeability was less than the required flux.

❖ Both the polymers showed good film-forming properties and the method adopted was satisfactory with folding endurance of 299 and 297 for optimized formulations of naproxen using gelatin and jackfruit mucilage.

❖ **Effect of polymer (gelatin) on the transdermal patch:** With the increase in concentration of gelatin the release rate of the drug was decreased with an increase in thickness. Hence optimum quantity of gelatin (2%) was used.

❖ **Effect of plasticizer (glycerine) on the transdermal patch:** As the concentration of glycerine was increased there was an increase in the release rate. But further increase in the concentration of glycerine showed higher moisture uptake making the patch brittle due to the hygroscopic nature of the glycerine. Hence attempts were made for the selection of the plasticizer in order to get a flexible patch with good drug holding property.

❖ **Effect of penetration enhancer on the transdermal patch:** 0.5% of DMSO was added as penetration enhancer to the formulations prepared using jackfruit mucilage as the release was not constant.

❖ Drug-excipient compatibility was evaluated using FTIR spectra and it was observed that there is no chemical interactions and functional alteration between the drug and excipient.

❖ The drug distribution was uniform with cumulative % drug release of 93.4% for Naproxen patch using gelatin and 88% Naproxen patch using jackfruit mucilage. In order to know the mechanism of the drug release, data were plotted accordingly for Zero order, First order, Higuchi plot and Korsmeyer peppas plot with R^2 values shown in tables 4.8.1 and 4.9.1. From the release studies, it was observed that both the formulations followed First order release with non-fickian diffusion mechanism and with an increase in proportion of glycerine the release of the drug increased with potential drug delivery, further increase in the glycerine concentration caused brittleness of the patch. Hence f8 formulations were optimized for both the patches but while comparing both the optimized formulations the patch prepared using gelatin showed greater release when compared to patch prepared using jackfruit mucilage. And it can be the best alternative over marketed preparations.

CONCLUSION:

The patches were successfully prepared with both the polymers and among all, the best formulation with gelatin was f8 and with Jackfruit mucilage f8. The release of the drug was sustained up to 24 hrs following first-order kinetics with non-fickian mechanism. Hence from the kinetic data and the release rate of the drug it can be concluded that TDDS patch with gelatin showed greater sustain release when compared to TDDS patch with Jackfruit mucilage and can be a better alternative for other topical routes.

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REFERENCES:

1. Richa Sachan, Meenakshi Bajpai.TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW.International Journal of Research and Development in Pharmacy and Life Sciences. December - January 2013, Vol. 3, No.1, pp 748-765.

2. Prit Lakhani*, Rishabh Bahl, and Piyush Bafna. International journal of pharmaceutical sciences and research a review on transdermal patches: physiochemical and *in-vitro* evaluation methods. Vol. 6(5): 1826-36.2014.
3. Audumbar Digambar Mali*, Ritesh Bathe, and Manojkumar Patil.An updated review of transdermal drug delivery systems.International Journal of Advances in Scientific Research 2015; 1(06): 244-254.
4. Harun Rasheed Shaik, HariBabu R, KhajaMohiddin Md, Vineela J. Transdermal Drug Delivery System - Simplified Medication Regimen - A Review. Research Journal of Pharmaceutical, Biological, and Chemical Sciences, 2011; 2(4): 223-238.
5. Dhiman Sonia, Singh Thakur Gurjeet, Rehni Ashish Kumar. Transdermal Patches: A Recent Approach to New Drug Delivery System. Int J Pharm Pharm Sci, 2011; 3(5):26-34.
6. Sharma Ajay, Saini Seema, Rana AC. Transdermal Drug Delivery System: A Review. International Journal of Research in Pharmaceutical and Biomedical, 2013; 4(1): 286-292.
7. Saini Nitin, Bajaj Anshul. Review Article Recent Trend in Transdermal Drug Delivery System and Advancements in Drug Delivery through Skin. International Journal of Research in Pharmaceutical and Biosciences, 2014; 4(1): 5-14.
8. Hadgraft J, Guy R. H. Transdermal Drug Delivery.2nd ed. New York: Marcel Dekker, 35. P.14-16.
9. Sandhu Premjeet*, Ajay Bilandi, Kataria Sahil and Middha Akanksha. TRANSDERMAL DRUG DELIVERY SYSTEM (PATCHES), APPLICATIONS IN PRESENT SCENARIO.INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY.2011, 1(4)
10. Shingade GM1, Aamer Quazi1, Sabale PM2, Grampurohit ND2, Gadhave MV2, Jadhav SL2, Gaikwad DD2REVIEW ON: RECENT TREND ON TRANSDERMAL DRUG DELIVERY SYSTEM.Journal of Drug Delivery & Therapeutics; 2012, 2(1)
11. Lincy John. Review of Transdermal Drug Delivery System.International Journal of Pharma Research and Health Sciences .Volume 2 (4), 2014, Page-261-272
12. Abdul Hafeez, Dr. Upendra Jain, Jagpal Singh, Arun Maurya, Lakhan Rana.Recent Advances in Transdermal Drug Delivery System (TDDS): An Overview.Journal of Scientific and Innovative Research 2013; 2 (3): 695-709
13. Pravin Gavali, Atul, Gaikwad, Radhika P.R, Sivakumar T, Design and Development of Hydroxypropyl Methylcellulose-based polymeric film of Enalapril Maleate, International Journal Of Pharmtech Research, 2010, 2(1), 274-282.
14. Koteshwar K.B, Udupa N, and Vasantha Kumar, Design and Evaluation of Captopril Transdermal Preparations, Indian Drugs, 15 (29), 680-685.
15. Yuvraj Singh Tanwar, Chetan Singh Chauhan, Anshu Sharma, Development and Evaluation of Carvedilol Transdermal Patches, Acta Pharm, 2007,57, 151–159.
16. Kamal Saroha, Bhavna Yadav, Benika Sharma, Transdermal Patch, A Discrete Dosage Form, International Journal of Current Pharma Research, 2011,3(3), 98-108.
17. N Aarti, Louk A.R.M.P, Russel.O.P and Richard H.G. Mechanism of oleic acid-induced skin permeation enhancement in vivo in humans, Jour. Control, Release 1995; 37: 299-306.
18. Verma PRP, Iyer SS. Transdermal delivery of propranolol using mixed grades of Eudragit: design and *in-vitro* and in vivo evaluation. Drug Dev. Ind. Pharm. 2000; 26: 471–476.
19. Sadashivaiah R, Dinesh BM, Patil UA, Desai BG, Raghu KS. Design and *in-vitro* evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers. Asian J Pharm 2008; 2:43-9.
20. V G Jamakandi et al., (2009) Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian Journal of Pharmaceutics -www.researchgate.net