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Research Article

FORMULATION AND EVALUATION OF IBUPROFEN TRANSDERMAL PATCHES

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ABSTRACT:
The purpose of this research was to develop a transdermal patches containing drug Ibuprofen with different ratios of Eudragit L 100, Sodium Alginate, Chitosan polymeric systems by the solvent casting method by using to Propylene Glycol as plasticizer. Different concentrations of Dichloromethane and Tween80 were used to enhance the transdermal permeation of Ibuprofen. The physicochemical compatibility of the drug and the polymers studied by differential scanning calorimetry and infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, folding endurance, percentage of moisture content. All prepared formulations indicated good physical stability. In-vitro permeation studies of formulations were performed by using Franz diffusion cells. Formulation F12 containing 200mg of Chitosan shows maximum drug permeation rate within 12hrs. Kinetic models were used to confirm release mechanism of the formulations. Ibuprofen release from the patch F12 followed Zero order kinetics and shows super case II transport mechanism.
Keywords: Ibuprofen, Chitosan, Propylene Glycol, FTIR.

INTRODUCTION:

A transdermal drug delivery system (TDDS) is a method of topical drug delivery that can provide a controlled systemic effect[1] .TDDS has advantages over oral drug administration, such as increasing patient compliance, avoiding first-pass metabolism, sustaining drug delivery, minimizing patient variability, maintaining constant and prolonged drug administration in plasma and easily discontinuing drug administration if an allergic reaction or poisoning occurs[2]. This route can also avoid drugrelated side effects such as gastric irritation. In transdermal delivery, the drug must have a small molecular size, adequate solubility in the carrier, short half life, low dose, and suitable lipophilicity[3].One of the dosage forms in the transdermal drug delivery system is a patch[4]. However, the stratum corneum on the skin becomes a barrier to the transdermal patch; thus, only drugs with small molecules can easily penetrate the stratum corneum, but this can also be overcome by adding enhancers[5]. Therefore, patch effectiveness is determined by the ability of drugs to be released from the patch matrix and penetrate the stratum corneum. The drug particles must first be dissolved to form molecules that can diffuse through the matrix, and then the drug will penetrate through the skin[6]. The advantages of having a Transdermal Drug Delivery System (TDDS) include that, unlike the limited controlled release of the oral and intravenous routes, TDDS provides a stable infusion of the drug over a long period of time, suitable for drugs with short biological half-lives that require frequent dosing, leading to on improving patient compliance. In addition, therapeutic failure or side effects frequently associated with intermittent dosing for chronic disease can be avoided using this route[7].

MATERIALS & METHODS USED:

Ibuprofen API was procured from Norm Life Sciences Pharma Private Limited, and Eudragit L 100, Sodium Alginate, Chitosan, Propylene Glycol, Dichloromethane, Tween 80 were procured from BMR Chemicals.

Determination of drug-excipient compatibility

FTIR: In the preparation of film formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug, preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Ibuprofen and the selected polymers. The pure drug and drug with excipient were scanned separately.

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Procedure: Potassium bromide was mixed with drug and/or polymer and the spectra were taken. FT-IR spectrum of Ibuprofen was compared with FT-IR spectra of Ibuprofen with polymer. Disappearance of Ibuprofen peaks or shifting of peak in any of the spectra was studied.

Analytical Methods:

Preparation of Solutions:

Phosphate buffer (pH 7.4) solution: 50 ml of 0.2 M potassium dihydrogen phosphate was taken in 200 ml volumetric flask, to which 31.9 ml of 0.2M sodium hydroxide solution was added and the volume was made up to the mark with distilled water. >

Potassium dihydrogen phosphate (0.2M) solution: potassium dihydrogen phosphate (27.218 g) was added to 1000 ml volumetric flask containing distilled Water and the volume was made up to the mark with distilled water.

Sodium hydroxide (0.2M) solution: Sodium hydroxide (8g) was added to 1000 ml volumetric flask containing distilled water and the volume was made up to the mark with distilled water

UV Scan for determination of λmax of drug:

100mg of drug sample was dissolved in suitable organic solvent and dissolved in 100ml (1000µg/ml) 7.4pH phosphate buffer. From the above stock solution-I , 10ml solution was diluted and volume was made up to 100ml 7.4 pH phosphate buffer (100µg/ml- Stock solution II). From the above stock solution-II , 1ml solution was diluted and volume was made up to 10ml of 7.4 pH phosphate buffer (10µg/ml- Stock solution III) which was spectroscopically scanned in UV spectroscopy at 200-400nm & wavelength at maximum absorbance was note downed.

Calibration curve of drug in 7.4 pH Phosphate buffer solution:

100 mg of drug was dissolved in organic solvent in which drug is soluble and make upto 100 ml with 7.4 pH phosphate buffer. (Primary stock solution). From the above primary stock solution, 10 ml solution was diluted and volume was made up to 100 ml 7.4 pH phosphate buffer (Secondary Stock solution). From the above secondary stock solution, 2-12 µg/ml concentration were prepared by using 7.4 pH phosphate buffer. The absorbance of above samples were analyzed at 222 nm.

PREPARATION OF IBUPROFENTRANSDERMAL PATCHES

The patches are prepared according to the following procedure of solvent casting method 51,52,80,81

The step wise procedure is as follows

- Accurately weighed Polymers were dissolved in 10 ml of solvent.
- Stirred in a magnetic stirrer for 60 min.
- The Ibuprofen was taken according to the working formula was weighed and dissolved in 5 ml solvent.
- The drug solution was mixed to polymer solution and stirred on magnetic stirrer for 15 min.
- The plasticizer and Penetration enhancers was added to drug polymer mixture.
- The mixed solution was sonicated for 20 min to remove any entrapped air bubbles.
- The final mixture was transferred to petri plates.
- The petri plates are covered with funnel in inverted position to gradual evaporation of dryness.
- After complete drying, the patches were recovered and stored in dessicator for further In vitro studies.

Note: 6.25 sq.cm buccal films containing 200 mg of Ibuprofen.

Calculation of dose for Ibuprofen:

The dose of Ibuprofen is 200 mg. Therefore, amount of Ibuprofen required in

2cm x 4cm=8cm2 film is 200 mg.

- Length of glass plate =4 cm.
- Width of glass plate =4 cm.
- Area of the plate =16 cm2.
- No. of 8cm2 films present whole plate =16/8 =2 films.
- Therefore, each films contains 200 mg of drug
- 2 films contain 400 mg drug (200*2=400mg).
- So, the Labelled claim of drug = 200 mg.

Table.1 Formulation table

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F1	F1	F1
Ibuprofen	400	400	400	400	400	400	400	400	400	400	400	400
Eudragit L 100	50	100	150	200	-	-	-	-	-	-	-	-
Sodium Alginate	-	-	-	-	50	100	150	200	-	-	-	-
Chitosan	-	-	-	-	-	-	-	-	50	100	150	200
Propylene Glycol(ml)	40	40	40	40	40	40	40	40	40	40	40	40
Dichloromethane (ml)	10	10	10	10	10	10	10	10	10	10	10	10
Tween 80 (ml)	10	10	10	10	10	10	10	10	10	10	10	10

EVALUATION OF IBUPROFENTRANSDERMAL PATCHES

The prepared transdermal patches were evaluated for the following;

Film Thickness

The thickness of films was measured by taking the 3 patches from each formulation and measured at different places using a Screw gauge and mean values were calculated.

Weight Variation

Weight variation was checked and studied by individually weighing 3 randomly selected films from the each formulation. Such determination was performed for each formulation.

Folding Endurance

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value.

Determination of Drug Content in the Film

The patches (4sq.cm of area) were cut and added to a beaker containing 100ml of phosphate buffered saline of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (containing no drug) at 222 nm spectrophotometrically. The experiment was repeated to validate the result.

Percentage of Moisture Content

The individually weighed patches formulation were and kept in desiccator containing anhydrous calcium chloride at room temperature for 3days. And then percentage of moisture content was calculated.

Percentage of Moisture Uptake

At room temperature weighed patches were kept in a desiccator for 24hours,then taken out and kept and exposed about 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator still a constant weight for the film was obtained.

In Vitro Drug Diffusion Studies

Release Kinetics

Data obtained from the In vitro formulations were fitted to various kinetic equations such As Zero order, First order, Higuchi model, Korsmeyer peppas model.

Zero order equation

$Q = Q0 – k0t$

First order equation

$\ln Q = \ln Q0 – kt$

Higuchi equation

$Q = k2t1/2$

Korsemeyers Peppas equation

$Q/Q0 = ktn$

RESULTS AND DISCUSSION

FT-IR spectrum and values

Pure Drug

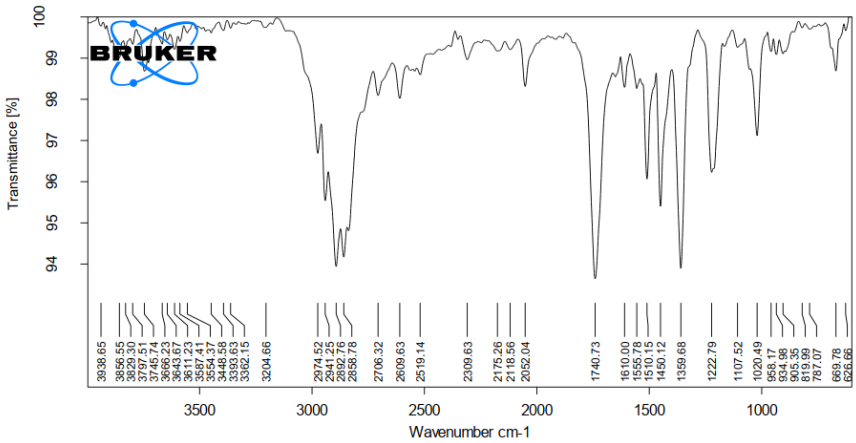

Figure.1 IR spectrum of pure Ibuprofen

Optimized

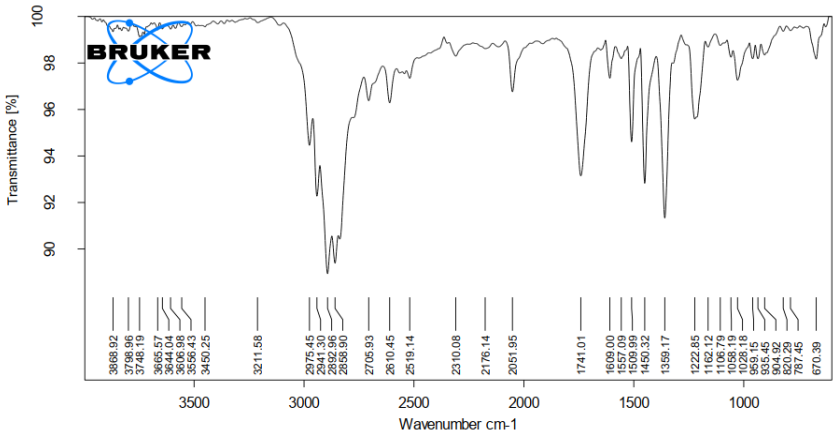

Figure.2 IR spectrum of Drug + excipients

Discussion: From the compatibility studies it was concluded that the functional groups that were presented in the pure drug were present in the optimized formulation with very minute changes, from this we can concluded that the drug and excipients have no interactions.

ANALYTICAL METHODS

Determination of λmax of Ibuprofen in pH 7.4 phosphate buffer solution

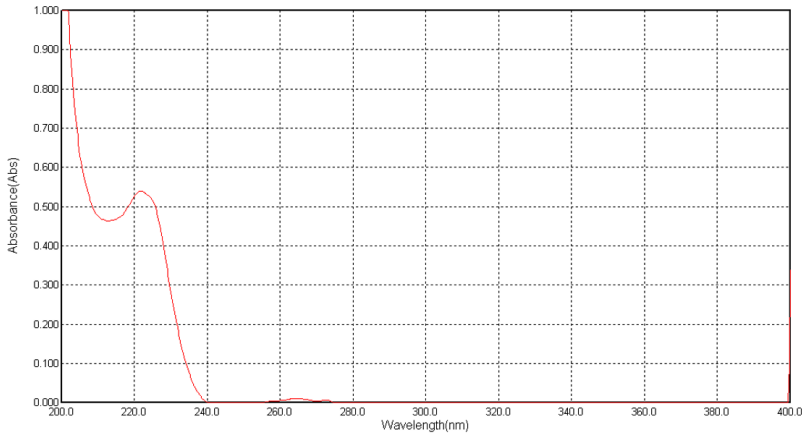

Figure.3 UV spectrum of Ibuprofen in 222nm

Discussion: From the UV spectral analysis of Ibuprofen in 10µg/ml it was observed that the Ibuprofen has 222 nm.

Calibration curve of pure drug (Ibuprofen) in pH 7.4 buffer solution

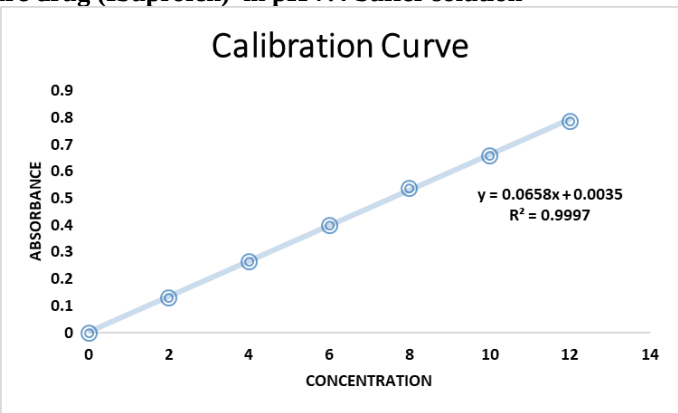

Figure.4 Calibration curve of Ibuprofen in pH 7.4 buffer solution

Discussion: Calibration curve of Ibuprofen was constructed in pH 7.4 buffer at maximum wavelength of 222 nm and analyzed for regression analysis. The regression line was defined by its slope (m) and its intercept (C) for normal regression analysis was found as 0.065 and 0.003, respectively, with regression coefficient of 0.999 respectively.

EVALUATION OF TRANSDERMAL PATCHES

Thickness uniformity

Table : Thickness uniformity of F1 to F12 patch formulations

Formulation code	Thickness (mm)
F1	0.079±0.02
F2	0.081±0.07
F3	0.093±0.06
F4	0.085±0.04
F5	0.067±0.03
F6	0.071±0.07
F7	0.078±0.06
F8	0.082±0.06
F9	0.061±0.04
F10	0.074±0.04
F11	0.086±0.04
F12	0.095±0.04

*Standard deviation, n = 2

Discussion:

The thickness of film was measured at different points and the average thickness was noted. The result indicates that there was no much difference in the thickness within the formulations and it was found to vary from 0.061±0.04 mm to 0.095±0.04 mm with low standard deviations.

Weight uniformity

Table.2 Weight uniformity of F1 to F12 patch formulations

Formulation code	% Weight variation
F1	1.15±0.42
F2	1.74±0.69
F3	1.62±0.75
F4	1.05±0.43
F5	1.64±0.29
F6	1.57±0.75
F7	1.69±0.41
F8	1.54±0.69
F9	1.24±0.75
F10	1.78±0.49
F11	1.16±0.04
F12	1.45±0.43

*Standard deviation, n = 2

Discussion: The films exhibited uniform weight variation ranging from 0.005 to 0.964% with low standard deviation values.

Folding endurance

Table.3 Folding endurance of F_1 to F12 patch formulations

Formulation code	Folding endurance
F1	147±7
F2	159±6
F3	167±2
F4	209±4
F5	194±3
F6	214±4
F7	198±9
F8	204±1
F9	197±1
F10	216±2
F11	242±5
F12	267±3

Discussion:
Folding endurance of formulated Ibuprofen transdermal patches (F1 to F12) was found in the range 147±7-267±3.

Percentage moisture content

Table.4 Percentage moisture content of F_1 to F12 patch formulations

Formulation code	% Moisture Content
F1	2.02±0.15
F2	2.31±0.21
F3	2.12±0.19
F4	2.69±0.12
F5	2.76±0.16
F6	3.27±0.17
F7	2.34±0.24
F8	2.69±0.36
F9	2.57±0.28
F10	2.67±0.12
F11	2.78±0.34
F12	2.95±0.19

Discussion: Percentage moisture content of formulated Ibuprofen transdermal patches (F1 to F12) was found in the range 2.02±0.15 to 2.95±0.19.

Percentage moisture uptake

Table.5 Percentage moisture uptake of F_1 to F4T3 patch formulations

Formulation code	% Moisture uptake
F1	3.42±0.45
F2	3.06±0.34
F3	3.16±0.18
F4	3.96±0.67
F5	4.76±0.45
F6	5.03±0.26
F7	3.42±0.85
F8	4.10±0.42
F9	4.76±0.36
F10	5.48±0.41
F11	5.94±0.24
F12	6.27±0.16

Discussion: Percentage moisture uptake of formulated Ibuprofen transdermals patches (F_1 to F12) was found in the range 3.06±0.34 to 6.27±0.16.

Drug content

Table. 6 Percentage of drug content of F_1 to F12 formulation

Formulation code	% Drug content
F1	94.52±1.14%
F2	95.43±1.45%
F3	96.46±1.37%
F4	97.76±1.21%
F5	94.35±1.95%
F6	95.04±1.24%
F7	97.06±1.45%
F8	98.42±1.37%
F9	96.46±1.45%
F10	97.12±1.84%
F11	98.45±1.24%
F12	99.37±1.49%

Discussion: Percentage drug content of formulated Ibuprofen transdermals patches (F_1 to F12) was found in the range 94.35±1.95% to 99.37±1.49%.

IN VITRO DRUG DIFFUSION STUDY

Table.7 In-vitro diffusion profile of Ibuprofen transdermal patch (F_{1-F3})

Time(hrs)	F1	F2	F3	F4
0	0	0	0	0
1	19.17±1.59	24.20±1.63	27.43±1.15	30.64±1.52
2	28.52±1.62	30.45±1.24	35.44±1.61	38.19±1.42
3	34.46±1.14	38.37±1.15	40.15±1.70	43.42±1.63
4	42.20±1.20	46.12±1.79	48.37±1.95	50.92±1.01
6	50.67±1.36	53.38±1.63	56.20±1.61	58.96±1.16
8	59.12±1.20	65.25±1.25	67.45±1.53	69.37±1.19
10	63.36±1.14	70.15±1.41	73.34±1.42	76.07±1.42
12	69.45±1.52	76.45±1.76	79.12±1.16	82.34±1.63

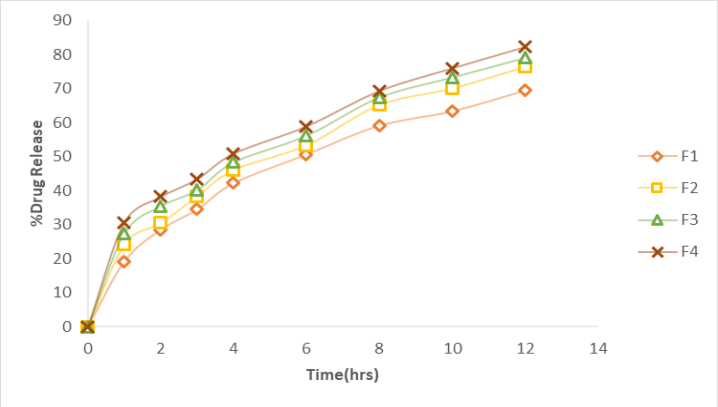

Figure.5 Percentage drug release of Ibuprofen TDDS (F1- F4)

Discussion: Total 4 formulations were formulated using Eudragit L 100 as polymer, Propylene Glycol as plasticizer. From the in vitro drug release studies, F1 formualtion is designed using Eudragit L 100 in the amount of 50mg which shows 69.45±1.52% of drug release at the end of 12hrs.

Whereas F2 formulation is designed using Eudragit L 100 in the amount of 100mg of which shows 76.45±1.76% of drug release at the end of 12hrs.

While F3 formulation is designed using Eudragit L 100 in the amount of 150mg of which shows 79.12±1.16% of drug release at the end of 12hrs.

While F4 formulation is designed using Eudragit L 100 in the amount of 200mg of which shows 82.34±1.63% of drug release at the end of 12hrs.

Table.8 In-vitro diffusion profile of Ibuprofen transdermal patch (F5-F8)

Time(hrs)	F5	F6	F7	F8
0	0	0	0	0
1	13.64±1.52	19.75±1.23	23.39±1.29	27.52±1.15
2	23.19±1.42	26.94±1.41	36.95±1.61	39.63±1.47
3	32.42±1.63	34.17±1.67	49.27±1.42	51.05±1.20
4	40.92±1.01	46.05±1.59	56.19±1.35	60.75±1.45
6	48.96±1.16	59.31±1.36	62.46±1.69	68.04±1.18
8	59.37±1.19	66.32±1.52	75.09±1.52	75.35±1.26
10	66.07±1.42	72.91±1.41	82.16±1.44	86.09±1.48
12	79.34±1.63	86.35±1.26	97.53±1.71	97.87±1.13

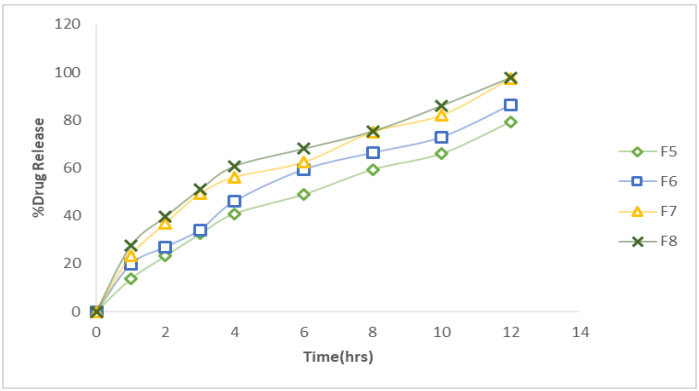

Figure.6 Percentage drug release of Ibuprofen TDDS (F5-F8)

Discussion: From the in vitro drug release studies, F5 formulation is designed using Sodium Alginate in the amount of 50mg which shows 79.34±1.63% of drug release at the end of 12hrs.

Whereas F6 formulation is designed using Sodium Alginate in the amount of 100mg of which shows 86.35±1.26% of drug release at the end of 12hrs.

While F7 formulation is designed using Sodium Alginate in the amount of 150mg of which shows 97.53±1.71% of drug release at the end of 12hrs.

While F8 formulation is designed using Sodium Alginate in the amount of 200mg of which shows 97.87±1.13% of drug release at the end of 12hrs.

Table.9 In-vitro diffusion profile of Ibuprofen transdermal patch (F9-F12)

Time(hrs)	F9	F10	F11	F12
0	0	0	0	0
1	21.64±1.52	25.75±1.23	29.39±1.29	34.52±1.59
2	31.19±1.42	37.94±1.41	40.95±1.61	42.63±1.26
3	47.42±1.63	49.17±1.67	48.27±1.42	53.05±1.74
4	56.92±1.01	58.05±1.59	61.19±1.35	65.75±1.35
6	63.96±1.16	67.31±1.36	69.46±1.69	73.04±1.48
8	75.37±1.19	78.32±1.52	80.09±1.52	82.35±1.27
10	86.07±1.42	89.91±1.41	89.16±1.44	92.09±1.21
12	93.34±1.63	95.35±1.26	97.53±1.71	99.17±1.45

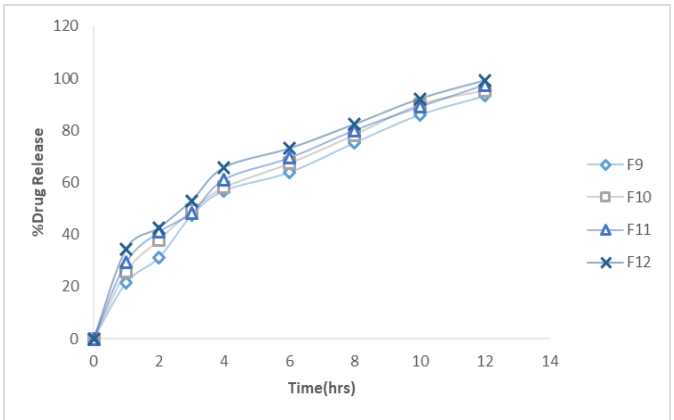

Figure.7 Percentage drug release of Ibuprofen TDDS (F9-F12)

Discussion: From the in vitro drug release studies, F9 formulation is designed using Chitosan in the amount of 50mg which shows 93.34±1.63% of drug release at the end of 12hrs.

Whereas F10 formulation is designed using Chitosan in the amount of 100mg of which shows 95.35±1.26% of drug release at the end of 12hrs.

While F11 formulation is designed using Chitosan in the amount of 150mg of which shows 97.53±1.71% of drug release at the end of 12hrs.

While F12 formulation is designed using Chitosan in the amount of 200mg of which shows 99.17±1.45% of drug release at the end of 12hrs.

Among all the formulations, it was observed that by increasing the concentration of polymer results in increase in the drug permeation rate. So F12 formulation is chosen as optimized formulation and further drug release kinetics were performed.

Drug Release Kinetics:

Zero order:

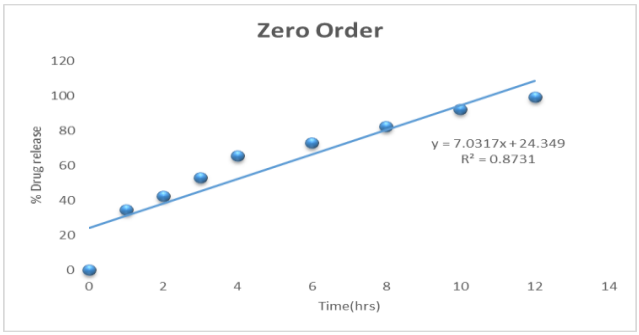

Figure.8 Zero order kinetics of optimized formulation (F12)

First order:

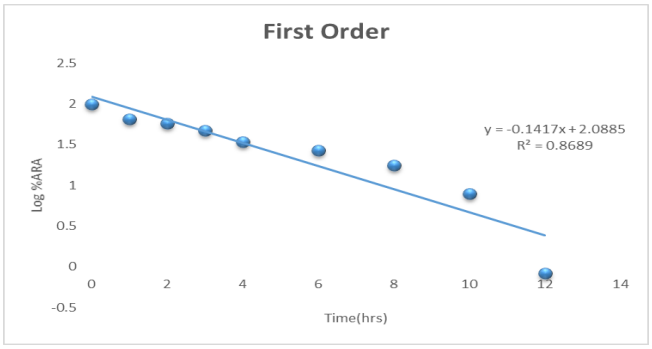

Figure.9 First order kinetics of optimized formulation (F12)

Higuchi plot:

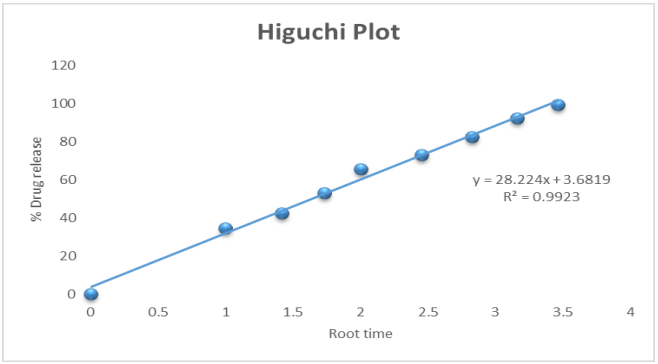

Figure.10 Higuchi plot of optimized formulation (F12)

Peppas plot:

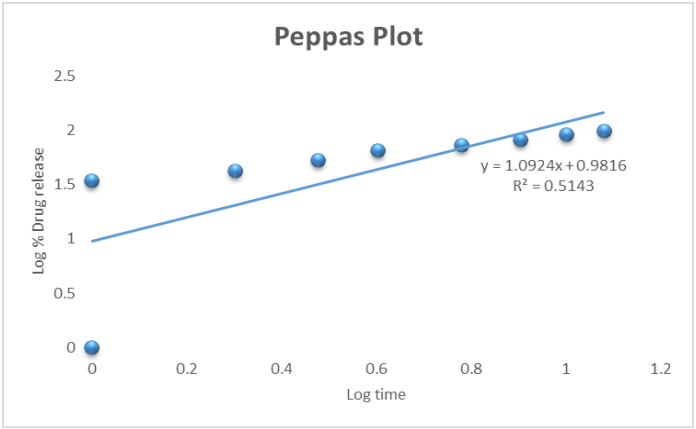

Figure.11 Peppas plot of optimized formulation (F12)

Discussion: The in vitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows R2 value 0.873. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The 'n' value is 1.092 for the optimised formulation (F12) i.e., n value was n > 0.89 this indicates Super case II transport.

SUMMARY AND CONCLUSION

The following conclusions were drawn from results obtained.

A suitable UV Spectroscopy method for the analysis of Ibuprofen was developed. Ibuprofen showed maximum absorption at wave length 222 nm in isotonic phosphate buffer (pH 7.4) solutions. The R^2 value for the standard curve was found to be 0.999, which showed linear relationship between drug concentrations and absorbance values. Based on the preformulation studies the drug was suitable for making the transdermal formulation. Drug-polymer compatibility studies by FT-IR gave confirmation about their purity and showed no interaction between the drug and selected polymers.

Various formulations were developed by using polymers like Eudragit L 100, Sodium Alginate, Chitosan by solvent casting method with incorporation of penetration enhancer such as Propylene Glycol as plasticizer. Developed transdermal patches possessed the required physicochemical properties such as drug content uniformity, folding endurance, weight uniformity, thickness uniformity, percentage moisture uptake and percentage moisture content. Most of the batches shows high folding endurance values (more than 50) which indicate that the patches would be less brittle on its application to the skin, maintaining their integrity with general skin folding. A small amount of moisture in patch helps maintain stability and prevents the formation of dried and brittle patches. A greater amount, however, can lead to microbial contamination during storage. From the results of the drug content determination, it was inferred that there was proper distribution of drug in the patches and the deviations were within the acceptable In vitro studies concluded that F2 formulation containing Chitosan 200mg as polymer shows maximum drug release of 99.17±1.45% within 12h. F4 to F9 formulations were formulated with different concentrations of permeation enhancers (DMSO, Tween80) among them formulation F6 containing 15% of DMSO shows maximum drug permeation rate within 12h. Kinetic models were used to confirm release mechanism of the formulations. Ibuprofen release from the patch F12 followed Zero order kinetics and shows super case II transport mechanism.

REFERENCES:

1. Pathan IB, Setty CM. Chemical Penetration Enhancers for Transdermal Drug Delivery Systems. Trop J Pharm Res. 2009;8(2):173–9. doi: 10.4314/tjpr.v8i2.44527.
2. Patel DP, Setty CM, Mistry GN, Patel SL, Patel TJ, Mistry PC, et al. Development and Evaluation of Ethyl Cellulose-Based Transdermal Films of Furosemide for Improved In Vitro Skin Permeation. AAPS PharmSciTech. 2009;10(2):437–42. doi: 10.1208/s12249- 009-9224-3.
3. Baviskar DT, Parik VB, Jain DJ. Development of MatrixType Transdermal Delivery of Lornoxicam: In Vitro Evaluation and Pharmacodynamic and Pharmacokinetic Studies in Albino Rats. PDA J Pharm Sci Technol. 2014;67(1):9–22. doi: 10.5731/pdajpst.2013.00898.
4. Prajapati ST, Patel CG, Patel CN. Formulation and Evaluation of Transdermal Patch of Repaglinide. ISRN Pharm. 2011;1–9. doi: 10.5402/2011/651909.
5. Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum. Pharmaceutics. 2015;7(4):438–70. doi:10.3390/pharmaceutics7040438
6. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: An overview. Int J Pharm Sci Rev Res. 2010;3(2):49–54. doi: 10.4103/0973-8398.104828.
7. Rabiei M, Kashanian S, Samavati SS, Mcinnes SJP. Nanomaterial and advanced technologies in transdermal drug delivery. J Drug Target. 2019;0(0):1–12. doi: 10.1080/1061186X.2019.1693579.