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TRANSDERMAL MATRIX PATCH AS A TOOL FOR DELIVERY OF KETOPROFEN

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Abstract: In the present study attempt was made to develop a suitable matrix types Transdermal patch of Ketoprofen using blends of four type of polymers with combination of HPMC E5 LV with other three polymer Eudragit RS 100, Ethyl cellulose (EC), PVP and they were prepared by solvent evaporation method. PVA was used as backing membrane. Prepared formulations were subjected to various physicochemical evaluations like % moisture content, % moisture up take, Thickness, weight uniformity, drug content, Folding endurance, Flatness, in vitro permeation studies. Drug excipient interaction studies were carried out using Fourier Transform infrared (FTIR) spectroscopy technique. The compatibility study of Ketoprofen and polymers indicated that there was no interaction between them. *In Vitro* skin permeation studies were carried out in a Franz's diffusion cell. The *in vitro* diffusion of the drug from the formulations was studied using rat abdomen skin. The formulation containing hydrophilic polymer (HPMC E5 LV, Eudragit RS 100) showed more moisture content and moisture uptake while in the combination of hydrophilic and hydrophobic polymer (EC) it showed less moisture uptake and moisture content. The formulation contenting HPMC E5 LV and Eudragit RS 100 with 30 % w/w plasticiser showed the good appearance and good physicochemical properties and also follows the zero order release kinetic. So from whole study it can be concluded that above blend of polymers can form suitable matrix transdermal patch with good patient compliance.

Keywords: Matrix Patch, Ketoprofen, HPMC E5 LV, Eudragit RS 100, Solvent Evaporation Method, In vitro skin permeation study

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INTRODUCTION

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin deliver the drug through the skin at controlled rate to the systemic circulation. [1]

Transdermal drug delivery offers many advantages such as reduced side effects, less frequent a dministration to produce the desired constant plasma concentration associated with improved patient compliance, elimination of the first-pass effect, sustained drug delivery and interruptio n of treatment when necessary. [2] NSAID (Non steroidal anti inflammatory drugs) are mostly used for the preparation of Transdermal patches for treatment of pain or inflammation.

Ketoprofen is NSAIDS drug that is propionic acid derivatives. The anti-inflammatory effects of ketoprofen are believed to be due to inhibition cylooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Ketoprofen is a non- specific cyclooxygenase inhibitor and inhibition of COX-1 is thought to confer some of its side effects, such as GI upset and ulceration. [3] When administered orally. Administration of ketoprofen via the dermal route can bypass these disadvantages of the oral route and may maintain relatively consistent plasma levels for long term therapy from a single dose.

Main objective of study is to formulate matrix type Transdermal patch of ketoprofen and to avoid side effects associated with oral administration.

MATERIAL AND METHOD

Ketoprofen was received as a gift sample from Yarro Chem, mumbai . HPMC E5 LV , Eudragit RS 100, Ethyl cellulose, Polly vinyl pyrilidone(PVP) and Polly vinyl alcohol (PVA) were purches from S.D fines, vadodara. Methanol, chloroform and purches from Chemdyes , Rajkot

Method

Preparation of backing membrane

A 4% (w/v) solution of polyvinyl alcohol (PVA) in distilled water was prepared using mechanical stirrer. Then 2 ml of the solution was poured in both side open glass moulds, one side of which is previously covered by aluminium foil. It was placed in dryer at 60ºC±2º C for drying over a period of 6 hrs. After 6 hrs moulds were removed from dryer and air dried for 24 hrs. [4]

Preparation of Transdermal Patch: (Solvent Evaporation Technique) [5]

In the present work transdermal patch was prepared by the solvent evaporation method where, the drug was dissolved in the suitable solvent along with the polymer and plasticizer.

Permeation Enhancer was added to improve the flux of the final formulation in desired amount, if needed. To cast film clear solution was allowed to evaporate in a suitable apparatus under controlled evaporation using funnel over the apparatus at room temperature until it was dried.

Physicochemical compatibility

The compatibility between ketoprofen and polymers used in the patch was evaluated using FTIR. Physical mixtures were prepared to study the effect of sample manipulation. [6]

EVALUATION OF TRANSDERMAL PATCH

Physical appearance:

All the Transdermal patches were visually inspected for colour, clarity, flexibility and smoothness.

Thickness: [7]

The thickness of transdermal film was determined by micrometer screw gauge at different places. The average and standard deviation of five reading were calculated for each batch of drug loaded patch.

Uniformity of weight: [8]

Weight variation was studied by individually weighing 10randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination : [9]

The Transdermal patch was determined based on dry weight of drug and polymer used by means of a UV Spectrometry method. Different formulations were cut in to pieces dissolved separately in 10ml of phosphate buffer pH 7.4 and stirred for dissolve. Appropriate dilutions were made with phosphate buffer pH 7.4. The resulting solution were filtered with whatman filter paper and analyzed for content at 261.5 nm in UV spectrometer. Average reading of three films was taken as the content of drug in one formulation.

Moisture content: [10]

The prepared films were weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

% Moisture content = $\frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$

Moisture Uptake: [10]

Weighed films were kept in desiccators at room temperature for24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

% Moisture uptake = $\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} X100$

Flatness: [11]

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip was cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100

percent flatness = $\frac{I1 - I2}{I1} \times 100$

I2 = Final length of each strip

I1 = Initial length of each strip

Folding Endurance: [12]

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

In vitro permeation studies: [13] (**SIP/IAEC/03/2013-14**)

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and

donor compartment in a vertical diffusion cell such as Franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectro photometrically. Then the amount of drug permeated per centimetre square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug.

Experimental Condition: Diffusion Cell- Modified Franz Diffusion Cell Diffusion Medium- phosphate buffer (pH7.4) Volume of Receptor compartment – 40ml Sampling Volume – 2ml Temperature of water jacket- 37±0.5°C

Kinetic modelling: [14]

In order to understand the kinetics and mechanism of drug release, the results of in vitro drug release are fitted into various kinetic equations like zero order (cumulative % release vs. time), first order (log % drug remaining vs. time), Higuchi's model (cumulative % drug release vs. square root of time), Krosmeyer peppas plot (log of cumulative % drug release vs. log time). R^2 (coefficient of correlation) and n (Diffusion exponent) values were calculated for the linear curve obtained by regression analysis of the in vitro drug permeation plots.

RESULT AND DISCUSSION

The FTIR spectrum of the physical mixture was compatible with pure drug and placebo spectrum.

In the present study 12 formulations were prepared by varying the polymer ratio and plasticizer ratio.

Matrix type patch of ketoprofen prepared by solvent evaporation technique using combination of hydrophilic and hydrophobic polymer. The prepared patch from the HPMC and Eudragit RS 100 combination were smooth , uniform and flexible with good physical strength. The thickness, drug content, flatness, %moisture content & % moisture up take were evaluated from that the hydrophilic polymer shows the increases hydrophilic polymer concentration the %moisture content and % moisture up take were increases. In case of hydrophobic polymer Ethyl cellulose and hydrophilic polymer HPMC it shows different result. %moisture content and % moisture up take rate of that patches were decreases compare to hydrophilic polymers. In the other formulation of PVP and HPMC does not show any physical strength. Also the HPMC

and EC in combination did not show transference appearance of the patches were hazy. Also same in PVP and HPMC containing polymers

The thickness of patches was observed among each group. There was no significant difference in thickness. There is no significant difference in the drug content among the patches indicated content uniformity, these shows the uniform distribution of drug in patch.

The all batches shows the hundred percent flatness which indicates no amount of constriction of the patches.

The in vitro drug diffusion study was carried out in a modified Franz diffusion cell using phosphate buffer (pH7.4). The permeation rate were decreases in the concentration of HPMC E5 increases. Formulation F1, F2, F7&F8 the permeation rate of drug increase with increase in Eudragit amount

In the EC combination with HPMC E5 and PVP with HPMC E5 did not shows appropriate release because of the lesser physical strength.

Cumulative amount of drug released per cm^2 from the different patches varied ratio of HPMC E5 and Eudragit RS 100 (F1,F2,F7&F8) ,varied ratio of HPMC E5 and EC (F3,F4,F9&F10) , varied ratio of HPMC E5 and PVP (F5,F6,F11&F12) showed variable release patterns. The process of drug release in most of controlled release devices including Transdermal patches was governed by diffusion.

From the results the different parameters were evaluated. The Eudragit RL 100 polymer with HPMC E 5 LV shows good appearance and also good physicochemical characteristics also the drug diffusion of the batch F7 shows the zero order release of drug.

Conclusion:

The in vitro permeation study from matrix based Ketoprofen patch with Eudragit RL 100(2%), HPMC E5LV (3%) with PEG 400 (30%) as a plasticizer showed best results of evaluation parameters among all formulations. *In vitro* release study gave 100% drug release from patch up to 12 Hrs. from present study it can be concluded that this formulation of transdermal patch can be suitable dosage form in treatment of diseases like rheumatoid arthritis or ankylosing spondylitis.

Table : 1 Formulation Batch

Batch	Ketoprofen (mg)	HPMC E5 LV (%w/v)	Eudragit RS 100 (%w/v)	Ethyl Cellulose (%w/v)	PVP K30 (%w/v)	PEG 400 (%w/w)
F1	30	3	2			15
F2	30	4	1			15
F3	30	3		2		15
F4	30	4		1		15
F5	30	3			2	15
F6	30	4			1	15
F7	30	3	2			30
F8	30	4	1			30
F9	30	3		2		30
F10	30	4		1		30
F11	30	3			2	30
F12	30	4			1	30
Methanol: Chloroform (1:1)as a Solvent (5ml)			*% of total polymer weight			

Table : 2 Evaluation of Patches

Batch	Folding endurance	Transparency	Surface Texture	Thickness (mm)	Avg. Weight(mg)
F1	112±1.59	Medium	Smooth	0.32	235±1.05
F2	99 ±0.24	Medium	Smooth	0.31	235±0.07
F3	93±1.03	Hazy	Rough	0.32	237±0.01
F4	39±2.7	Hazy	Rough	0.35	237±0.19
F5	20 ±2.10	Hazy	Rough	0.33	226±0.08
F6	10±1.11	Hazy	Rough	0.35	230±0.03
F7	190 ±2.58	Transparent	smooth	0.34	236±0.07
F8	102±1.11	Medium	Smooth	0.34	233±0.03
F9	42±1.35	Hazy	Smooth	0.33	231±0.9
F10	70 ±0.24	Hazy	Rough	0.29	235±0.12
F11	117±1.03	Medium	Smooth	0.32	237±0.01
F12	79±3.7	Medium	Smooth	0.35	227±0.19

Table : 3 Evaluation of Patches

Batch	%moisture content	%moisture up take	%drug content	Flatness
F1	4.7±1.1	3.1±0.8	94.1	100
F2	3±0.2	2.04±0.007	92.78	100
F3	2.47±0.7	1.9±0.93	89.01	100
F4	3.7±0.2	3.0±0.01	89.06	100
F5	4.8±1.06	3.7±1.07	92.68	100
F6	2.1±0.14	2.0±1.02	84.86	100
F7	5.02±0.9	5.37±0.04	96.7	100
F8	3.88±1.2	1.8±0.24	94.26	100
F9	4.1±0.06	2.9±0.71	86.38	100
F10	2.8±1.08	2.5±0.7	90.7	100
F11	3.4±0.17	2.9±1.01	90.48	100
F12	2.7±0.19	3.1±1.27	93.87	100

Table : 4 Release Kinetic of all batches

	R^2			
Batch	zero	first	Higuchi	Kosmeyer peppes
F1	0.9629	0.655	0.9572	0.8997
F2	0.965	0.9783	0.8706	0.9178
F3	0.9843	0.7772	0.9789	0.9602
F4	0.9613	0.7946	0.9565	0.9594
F5	0.9789	0.7272	0.961	0.9348
F6	0.988	0.472	0.9767	0.5579
F7	0.9501	0.6958	0.9483	0.9436
F8	0.8813	0.6926	0.8965	0.8901
F9	0.9645	0.7486	0.978	0.9692
F10	0.9774	0.747	0.9958	0.9535
F11	0.9814	0.8508	0.9677	0.9766
F12	0.9906	0.8143	0.9764	0.984

Figure 1 Folding endurance

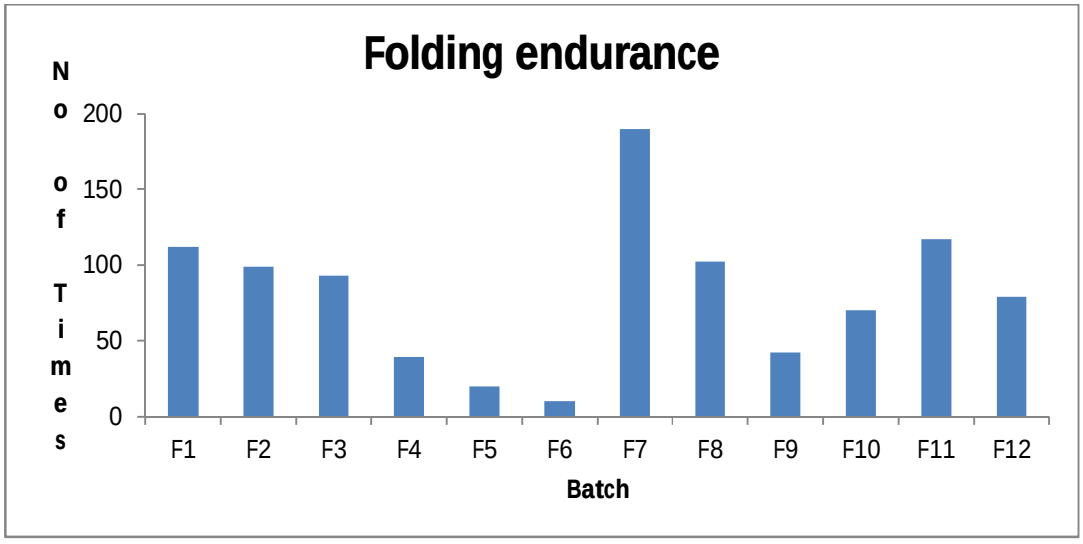


Figure 2 %moisture content and % moisture uptake

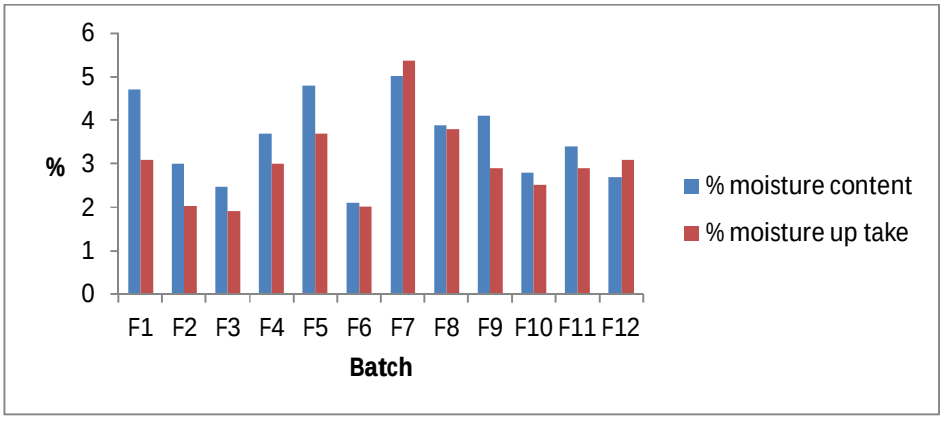


Figure 3 Diffusion profile F1-F6

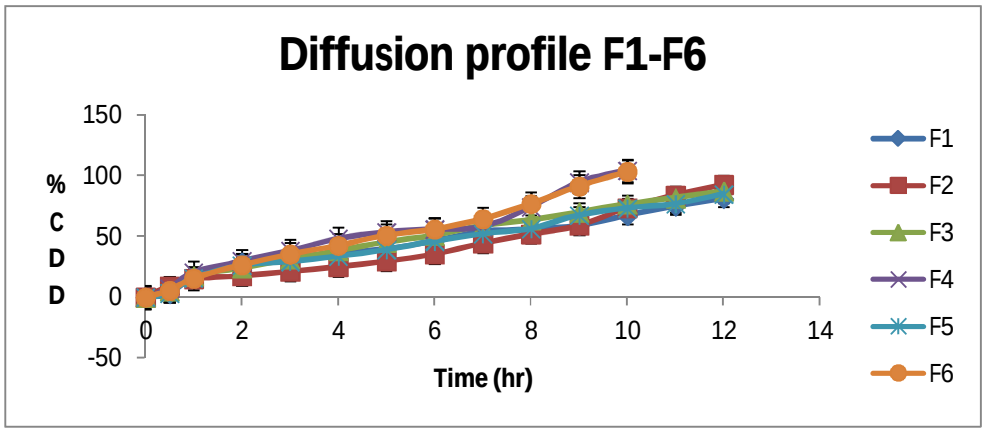


Figure 4 Diffusion profile F1-F6

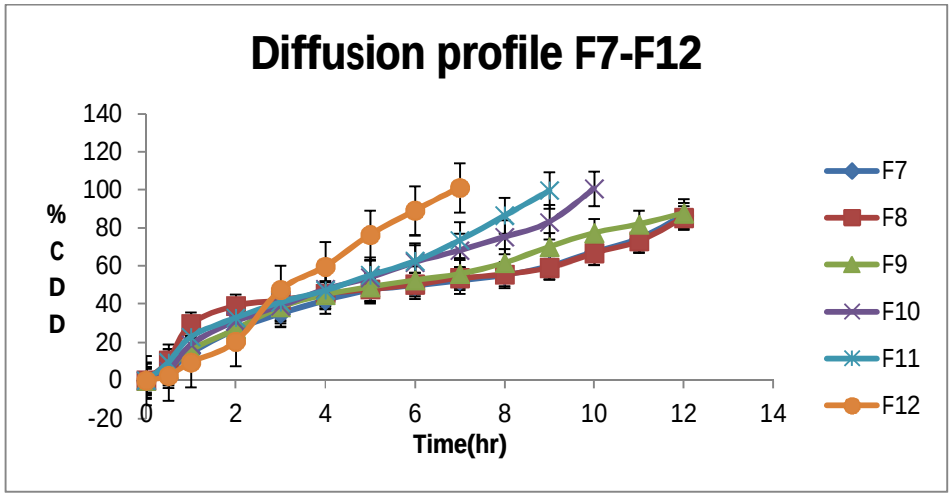
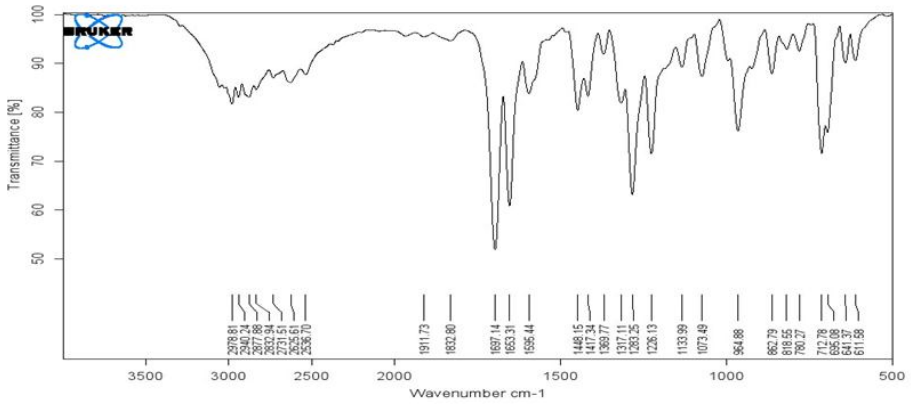
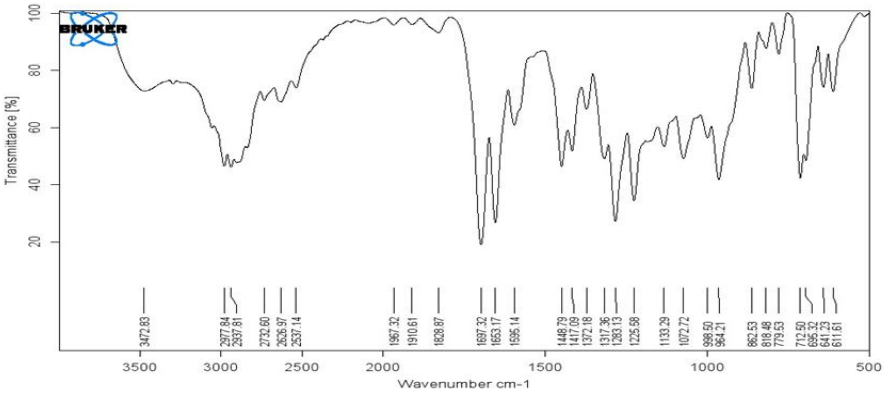


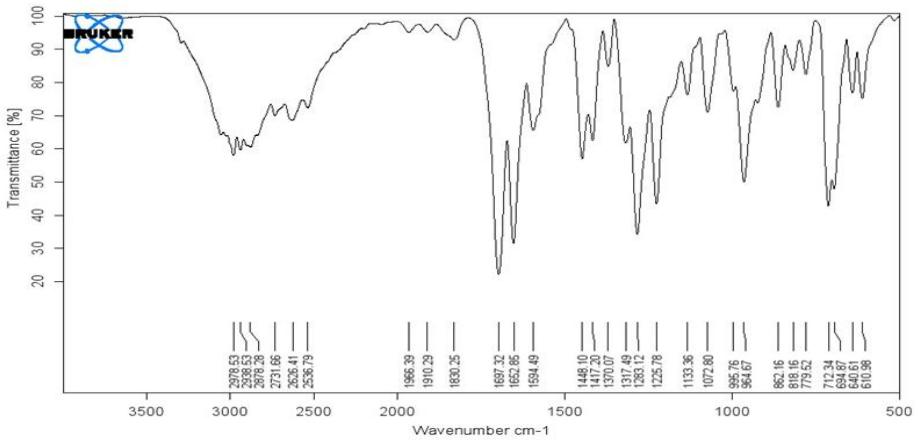
Figure 5 FTIR spectrum



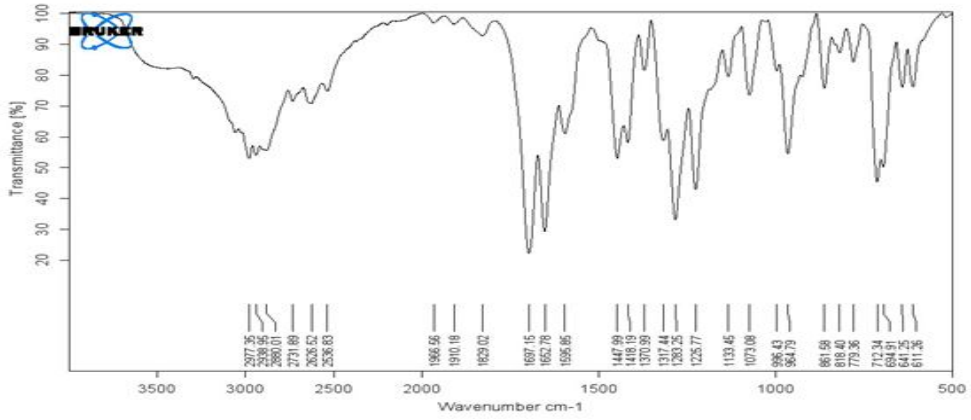
5.1 Ketoprofen



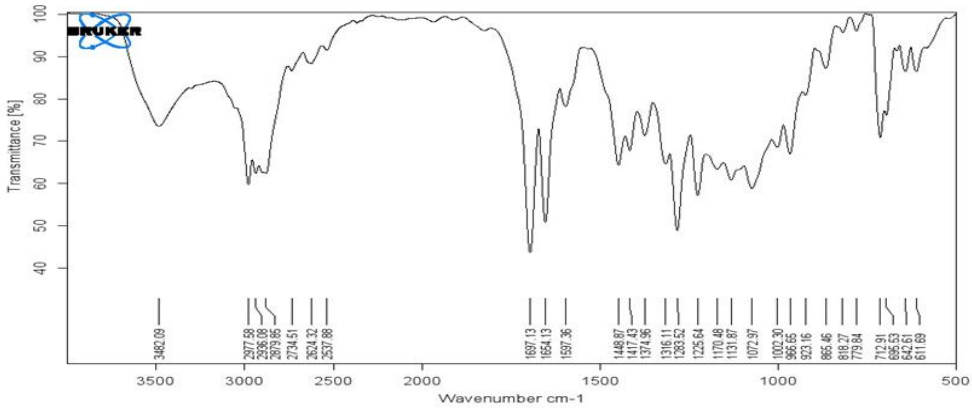
5.2 Ketoprofen + HPMC E5 LV= No interaction



5.3 Ketoprofen + Eudragit RS 100 = No Interaction



5.4 Ketoprofen + PVP K 30 = No Interaction



5.5 Ketoprofen + Polymer mixture= No interaction

REFERENCES

1. Arunachalam A *et al.*, "Transdermal Drug Delivery System: A Review," *Cur. Pharma Res,* 2010, 1(1), 70-81.

2. Dey S, Malgope A, "Preparation of Carvedilol Transdermal Patch and the Effect of Propylene Glycol on Permeation." *Int J Pharma and Pharma Sci,* 2010, 2(1), 137-143.

3. Igor S, Julia K, Galina R, Bertil A, Sabine K, Peter L, James P, Vinod S, Groot D, Dirk B and Jennifer D, " Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Ketoprofen." *J Pharma Sci*, 2012, 101(10), 3593-3603

4. Mukharjee B. et al., "A comparison between povidone-eudragit Transdermal dexomethosone matrix patch based on in vitro skin permeation." *Eur. J. Pharm. Biopharm,* 2004, 59, 475-483.

5. Prabhu L *et al*., "Design and Evaluation of Matrix Diffusion Controlled Transdermal Patches of Dexibupofen." *J. App. Re,* 2012,12(1),38-46.

6. Rama B, Shantha A, "Optimization of Methotrexate Travsdermal Patch: Effect of Variables on In-vitro, ex-vivo Permeation and Flux." *Int. J. pharm. Sci. Lett,* 2010, 2(2), 53-59.

7. Dandigi P, Sowjanya P, Tapas P, Bhavana D and Aravapalli A, "Design and Characterization of Diclofenac Diethylamine Transdermal Patch Using Silicone And Acrylic Adhesives Combination." *J Pharma Sci*, 2013, 21(6),1-14.

8. Comoglu T, Gonul N, Baykara T. "Preperation and in vitro Evaluation of Modified Release Ketoprofen Microsonges." *IL Ffarmaco*, 2003.58,101-106

9. Ramakanth S, Madhusudana C and Sudhakar Y, "Development and Evaluation of Transdermal drug delivery system of Atenolol." *Int. J. Res. Pharm. Sci.* 2012, 2(4),692-697.

10. Rajesh S and Sujith S, "Permeation Of Flurbiprofen Polymeric Films Through Human Cadaver Skin" *Int. J. Pharm Tech Res,* 2013, 5(1), 177-182.

11. Babua R, Pandit J, "Effect of Penetration Enhancers On The Release and Skin Permeation of Bupranolol From Reservoir-Type Transdermal Delivery Systems." *Int J Pharma*, 2005, 288, 325–334

12. Gupta JRD., Irchhiaya R, Garud N, Tripathi P, Dubey P and Patel JR, "Formulation and Evaluation of Matrix Type Transdermal Patches of Glibenclamide." *Int. J. Pharm. Sci. D. Res.* 2009, 1(1), 46-50.

13. Jirapornchai S, Prapaporn B, Wirach T, Garnpimol R and Wiwat P, "Characterization, In Vitro Release and Permeation Studies of Nicotine Transdermal Patches Prepared From Deproteinized Natural Rubber Latex Blends." *Chem eng res and design*, 2012, 90, 906–914.

14. Franz T, precutinious absorption : on the relevance of *in vitro* data, J. Invest. Dermatol.1975,34; 715-717.