"DEVELOPMENT AND OPTIMISATION OF TRANSDERMAL FORMULATIONS OF DICLOFENAC SODIUM"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of requirements for degree of

Bachelor of Pharmacy

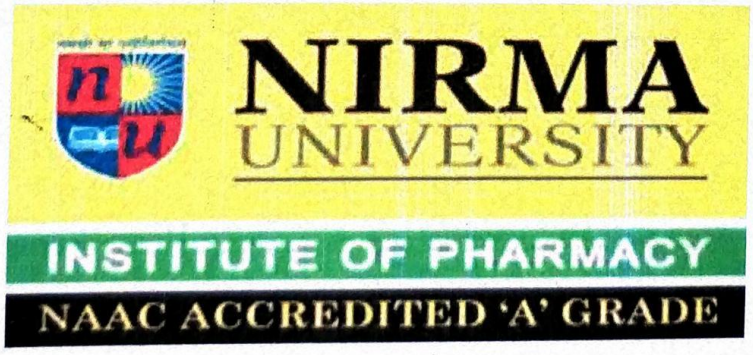
BY

SHAH NEEL A. (16BPH059)

Semester VIII

UNDER THE GUIDANCE OF

DR. MOHIT P SHAH



INSTITUTE OF PHARMACY
NIRMA UNIVERSITY
SARKHEJ-GANDHINAGAR HIGHWAY
AHMEDABAD-382481
GUJARAT, INDIA

APRIL 2020

CERTIFICATE

This is to certify that **"DEVELOPMENT AND OPTIMISATION OF TRANSDERMAL FORMULATIONS OF DICLOFENAC SODIUM"** is the bonafide work carried out by **SHAH NEEL A. (16BPH059)**, B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.

Guide:

Dr. Mohit P Shah
M.Pharm., Ph.D.,
Assistant professor,
Department of Pharmaceutics
Institute of Pharmacy,
Nirma University

Co-Guide:

Dr. Snehal Patel
M.Pharm., Ph.D.,
Assistant professor
Department of Pharmacology,
Institute of Pharmacy,
Nirma University

Dr. Tejal Shah
M.Pharm., Ph.D.,
Head, Department of Pharmaceutics
Institute of pharmacy,
Nirma University

15/7/2020

Prof. Manjunath Ghate
M.Pharm., Ph.D.,
Director,
Institute of Pharmacy,
Nirma University

Date: 25 / 04 / 2020

CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work entitled **"DEVELOPMENT AND OPTIMISATION OF TRANSDERMAL FORMULATIONS OF DICLOFENAC SODIUM"** submitted by **SHAH NEEL (16BPH059)**, B.Pharm semester VIII is a bonafide research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of "Dr. Mohit Shah and Dr. Snehal Patel". I am aware about the rules and regulations of plagiarism policy of Nirma University, Ahmedabad. According to that, the research work carried out by me is not reported anywhere as per best of my knowledge.

Shah Neel (16BPH059)
Institute of Pharmacy,
Nirma University
Sarkhej-Gandhinagar Highway,
Ahmedabad-382481
Gujarat, India

Guide:

Dr. Mohit P Shah
M.Pharm., Ph.D.,
Assistant professor,
Department of Pharmaceutics,
Institute of Pharmacy,
Nirma University

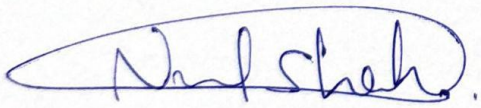
Co-Guide:

Dr. Snehal Patel
M.Pharm., Ph.D.,
Assistant professor,
Department of Pharmacology,
Institute of Pharmacy,
Nirma University

Date: 25 /04 / 2020

DECLARATION

I, **SHAH NEEL (16BPH059),** student of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled **"DEVELOPMENT AND OPTIMISATION OF TRANSDERMAL FORMULATIONS OF DICLOFENAC SODIUM"** is a result of culmination of my sincere efforts. I declare that submitted project is done solely by me and to the best of my knowledge , no such work is done by any other person for the award of degree or diploma or any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.



Shah Neel (16BPH059)
Institute of Pharmacy,
Nirma University
Sarkhej-Gandhinagar Highway,
Ahmedabad-382481
Gujarat, India

ACKNOWLEDGEMENTS

I would like to take opportunity firstly to thank Almighty for his constant shower of blessings in all myendeavors...

I would like to express my sincere thanks to all those concerned with my thesis as “Development and optimization of transdermal formulations of diclofenac sodium”, Also to all those who directly or indirectly assisted mein the completion of my thesis work.

I would also like to thank my parents and guardian for their timelysupport and their guidance for me. Their guidance and care because of which reaching to this stage oflife wouldn’t be possible.

In providing the fundamental picture to my thesis I would take this opportunity to express my heartilygratitude to my guide Dr. Mohit Shah Assistant professor, Department of pharmaceutics and co-guideDr. Snehal Patel Assistant professor, Department of Pharmacology, Institute of pharmacy,Nirma University to.

Their timely guidance and support provided shape to this project because of which I am truly grateful.

Lastly I would thank Dr. MANJUNATH GHATE sir Director, Institute of pharmacy, Nirma University for providing platform to showcase my talent regardingthis thesis.

INDEX

1) ABSTRACT:

The mainpurpose of this study was development and evaluation of the topical formulations that is gels and creams using the gelling agents like Carbopol and HPMC in two different ratios and two different bases for the cream that is bees wax and stearic acid. The drug which was chosen was Diclofenac Sodium which is a NSAIS and mostly used as analgesic. All the prepared formulations of gels and creams were tested and evaluation tests for physical appearance, stability, drug content were performed and all the formulations showed acceptable characteristics. The drug release of all the prepared batches were carried out by an apparatus called as Franz Diffusion cell. The optimized batch was obtained from the results of the evaluation tests and were further validated for its rheological properties.

2) INTRODUCTION:

Drug delivery to skin is a targeted and efficacious therapy for the skin related disorders. This particular route of administration is much common in use as it avoid the first pass metabolism, metabolic degradation and gastrointestinal ulceration. Because of the first pass metabolism, 20-45% of the dose that is given orally reaches into the circulation in the blood. Transdermal formulations have been proposed as topical application to combat this problem. Such prepared materials helps in suitable drug delivery also it is easily washable from the skin. The release of the drug from the prepared batches is dependent on the physicochemical parametersof the vehicles and the drug that were chosen used in the formula. Percutaneous absorption releases the drug from the product and the permeation occurs with the help of skin to reach target tissue in the body.

The drug employed is a potent inhibitor of both the cyclo oxygenase enzymes. This is sold in dosage forms like creams, gels, ointments, lotions and also as parentrals and oral dosage forms. It is used in the long term for musculoskeletal disorders like osteoarthritis, rheumatoid arthritis. As in the oral administrations it causes various side effects such as GIT ulceration, kidney and liver related problems, it is being administered more by the topical means. This transdermal drug delivery helps to overcome the side effects caused by oral administration and further it will also help in increasing its therapeutic efficacy.

This researchwas carried out to verify the cream and gel formulations. Two different formulations of cream were prepared with bees wax in one formulation and stearic acid in the other formulation along with the drug that is diclofenac sodium in both the creams. Similarly, two different formulations of gel were prepared using the two different ratios of gelling agents like Carbopol 934 P and HPMC. The evaluation tests of all the batches were carried out like drug content/release , physical appearance, Stability , homogeneity , grittiness, stability.

3) MATERIALS AND METHODS

3.1) MATERIALS

Diclofenac sodium, bees wax, stearic acid, Hydroxy Propyl Methyl Cellulose K4M, isopropyl alcohol, propylene glycol, liquid paraffin, borax, cetyl alcohol, sodium hydroxide, potassium hydroxide, glycerol, isopropyl myristate, distilled water.

3.2) METHODS OF PREPARATION

BATCH A

Needed amount of bees wax and liquid paraffin are taken in a porcelain dish and they heated to melt on a water bath so that oily phase is prepared.

In another porcelain dish needed amount of Borax and water were taken ,were heated to obtain the aqueous phase.

Both the mixtures were mixed by adding one phase into another and required quantity of diclofenac sodium was added with continuous stirring till a cream like consistency was obtained.

INGRIDIENTS	Quantity/20g(%w/w)
LIQUID PARAFFIN	40
BEES WAX	12
DICLOFENAC SODIUM	5
BORAX	1
PRESERVATIVE	0.1
DISTILLED WATER	q.s

Table 1

Table 1 – Formulation table for BATCH A

BATCH B-Procedure: Required quantity of stearic acid, cetyl alcohol and isopropyl myristate were taken in a porcelain dish and heated to melt all the ingridients.

In another beaker dissolve the sodium and potassium hydroxide in water, add glycerol and preservative and heatedfor obtaining aqueous phase.

Add alkali solution and required quantity of diclofenac sodium to the oily components with stirring with the help of glass rod to obtain desired consistency.

INGRIDIENTS	Quantity/ 20g(%w/w)
STEARIC ACID	15
CETYL ALCOHOL	0.5
DICLOFENAC SODIUM	5
ISOPROPYL MYRISTATE	3
NAOH	0.15
KOH	0.5
GLYCEROL	4
PRESERVATIVE	0.15
WATER	Q.S

Table 2

TABLE 2- Formulation table for BATCH B

BATCH C and D-Required quantity of drug mixed with required quantity of isopropyl alcohol to make it dissolve.Needed amount of PG (Propylene Gycol) was also made to dissolve in this solution.

Required amount of gelling agents and their combinations were added to the quantity sufficient amount of water which contains minute quantity of Nabisulfide to prevent oxidation and was dissolved while constant stirring.

Both the solutions were mixed in way that they would make up the desried weight and obtain a gel like consistency. It was allowed to stand for 24 hours.

INGRIDIENTS	Quantity/20g	
DICLOFENAC SODIUM	2%w/w	
ISOPROPYL ALCOHOL	1g	
PROPYLENE GLYCOL	1g	
CARBOPOL 934P:HPMC	01:03	
DISTILLED WATER	q.s	

TABLE 3

TABLE 3- Formulation table for BATCH C

INGRIDIENTS	%w/w
DICLOFENAC SODIUM	2%w/w
ISOPROPYL ALCOHOL	1g
PROPYLENE GLYCOL	1g
CARBOPOL 934P:HPMC	03:01
DISTILLED WATER	q.s

TABLE 4

TABLE 4- Formulation table for BATCH D

4) EVALUATION PARAMETERS

4.1) Physical evaluation

Bothbatches of gels and creams were visually analyzedin terms of their visual properties like colour, clarity, homogeneity and separation of phase.

Homogeneity , texture were evaluated by pressing a minute quantity of the formulated gels and creams between the index finger and the thumb.

Presence of coarse particles and consistency were used to evaluate the same.

4.2) Homogeneity

Prepared formulations were monitored in terms ofHomogeneity with the help of viewing analysis.

Further the tests in terms of Appearance, aggregation containment in the formulation were carried out.

4.3) Viscosity

The measurement of the viscosity can be done by using the instrument Brookfield viscometer.

The spindle number and the speed in the instrument is determined by trial and error method. The digital reading is ≥100% then speed , spindle number has to be decreased.

And vice versa is the case for digital reading≤10%.

FORMULATION	PHYSICAL APPEARANCE	TEXTURE	PHASE SEPARATION	HOMOGENEITY
BATCH A	OPAQUE	SMOOTH	NO	HOMOGENEOUS
BATCH B	OPAQUE	SMOOTH	NO	HOMOGENEOUS
BATCH C	TRANSPARENT	SMOOTH	NO	HOMOGENEOUS
BATCH D	TRANSPARENT	SMOOTH	NO	HOMOGENEOUS

TABLE 5 -PHYSICOCHEMICAL EVALUATION OF ALL 4 BATCHES

4.4) Stability study

This was done with the concept of Freeze-thaw cycle wherein the formulation was kept at -6°C and 45°C for 1 day each alternatively to complete one cycle.

This process was repeated for 3 times to complete 3 cycles . At the end of each cycle the formulation was observed for stability.

4.5) In vitro drug release

Franz-diffusion cells apparatus was used to carry out the tests.

Cellophane membrane was soaked for 12 hours in the prepared solution of phosphate buffer of pH value 7.4. 150 mg of the formulation was weighed on the membrane that

was held in chambers of donors and receptors in an area that was availed for the diffusion.

The apparatus was completely filled with help of a solution of Phosphate Buffer of pH value 7.4, laid on a hot plate with a magnetic bead inside it rotating at 100 RPM at the room temperature conditions with a variation of ±0.5°C.

The sampling was done for every 1 hour time interval and were replaced with the prepared phosphate buffer solution.

The samples were further analysed in UV spectrophotometer at the absorbance of 276nm.

4.5.1) Preparation of standard curve for in vitro drug release

The standard curve is generated by using UV spectroscopy.

For diclofenac sodium : A standard stock solution was prepared by solubilizing diclofenac sodium in water to make the concentration of 10µg/ml.

It was further diluted with water to make a series of concentration of 1, 2, 4, 6, 8, 10µg/ml.

The absorbance was found to be 276nm as per IP.

The calibration curve was plotted as absorbance vs concentration of diclofenac sodium to obtain the coefficient of correlation and the equation

TABLE- 6

CONCENTRATION(µg/ml)	ABSORBANCE (nm)
1	0.027
2	0.031
4	0.06
6	0.135
8	0.201
10	0.291

Table 6- Values of the absorbance for different series of concentrations for obtaining a standardcurve.

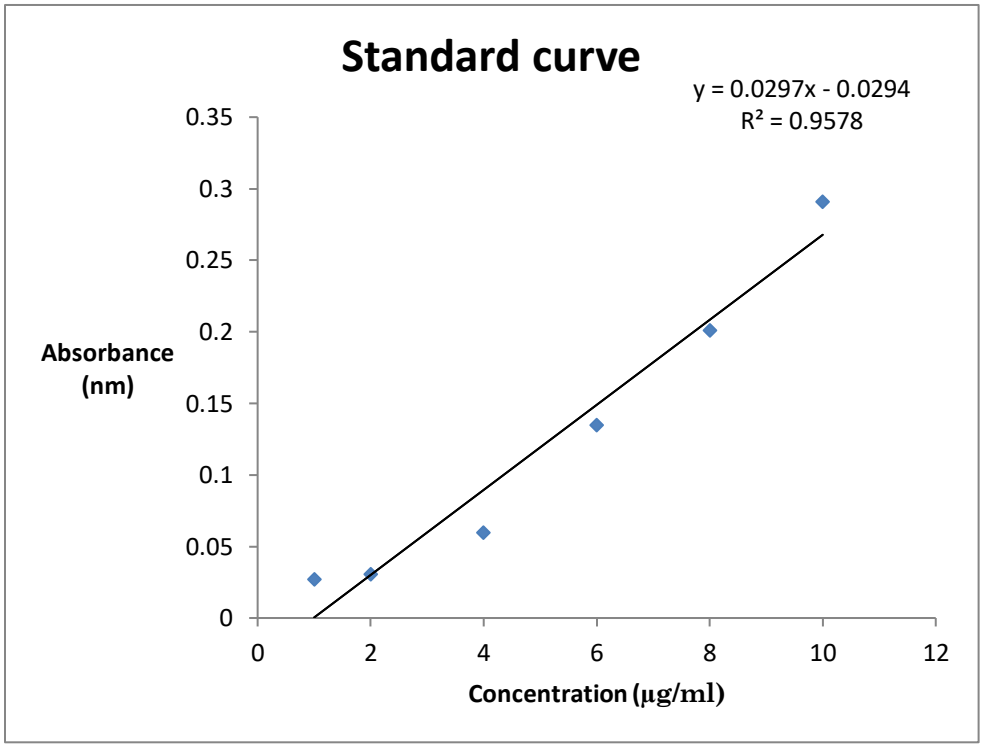


Figure 1 – absorbance v/s concentration

5)***Result and discussion***

Physical evaluation of all the prepared formulations.

The organoleptic properties like color, texture, physical appearance, homogeneity and phase separation are mentioned in table no. 5.

The evaluated results showed that both the prepared gels and creams had smooth texture and suitable for topical cosmetic appearance.

There was no phase separation in any of the formulation and all were homogeneous.

Stability study

Study for the stability of all batches were performed in which all the formulations were found to be stable as mentioned in the table no. 7

FORMULATION	AFTER 1ST CYCLE	AFTER 2ND CYCLE	AFTER 3RD CYCLE
BATCH A	+	+	+
BATCH B	+	+	+
BATCH C	+	+	+
BATCH D	+	+	+
STABLE = +	UNSTABLE = -		

Table 7- Stability studies of all 4 batches

In vitro drug release

The drug release study of creams of which Batch A was found to have lesser drug release than Batch B which can be seen in the table no. 8 and 9

The cumulative drug release of batch A and batch B can be seen in the figure 2 and 3 respectively.

Table no. 8

time	absorbance	concentration 5 ml(µg/ml)	concentration 5 ml (mg/ml)	concentration in 25 ml (mg/ml)	Cumulative concentration	% CDR
0.5 hr	1.94	67.897	0.068	0.339	0.339	4.526
1 hr	1.784	62.517	0.063	0.313	0.652	8.694
2 hr	2.134	74.586	0.075	0.373	1.025	13.667
3 hr	2.147	75.034	0.075	0.375	1.400	18.669
4 hr	2.369	82.690	0.083	0.413	1.814	24.182
5 hr	1.791	62.759	0.063	0.314	2.127	28.366

Table 8- In vitro drug release for Batch A

Table no. 9

time	absorbance	concentration 5 ml (µg/ml)	concentration 5 ml (mg/ml)	concentration in 25 ml (mg/ml)	Cumulative concentration	% CDR
0.5 hr	1.84	64.448	0.064	0.322	0.322	4.297
1 hr	1.962	68.655	0.069	0.343	0.666	8.874
2 hr	2.439	85.103	0.085	0.426	1.091	14.547
3 hr	2.684	93.552	0.094	0.468	1.559	20.784
4 hr	2.541	88.621	0.089	0.443	2.002	26.692
5 hr	2.145	74.966	0.075	0.375	2.377	31.690

Table 9- In vitro drug release for Batch B

Figure 2 cumulative % drug release for batch A

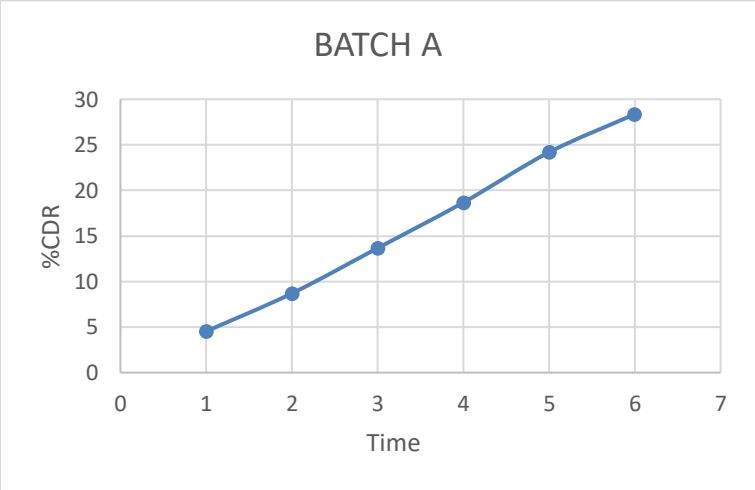
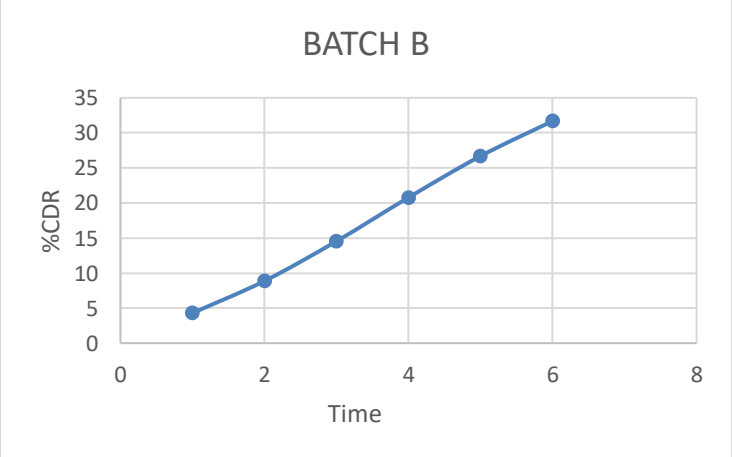


Figure 3 cumulative % drug release for batch B



On the other side, drug release study of gels of which Batch C was found to have better drug release than Batch D which can be seen in the table no. 10 and 11 respectively.

The cumulative drug release of batch C and batch D can be seen in the figure 4 and 5 respectively.

time	absorbance	concentration 5 ml (µg/ml)	concentration 5 ml (mg/ml)	concentration in 25 ml (mg/ml)	Cumulative concentration	% CDR
0.5 hr	1.572	55.207	0.055	0.276	0.276	6.134
1 hr	1.826	63.966	0.064	0.320	0.596	13.241
2 hr	2.389	83.379	0.083	0.417	1.013	22.506
3 hr	2.437	85.034	0.085	0.425	1.438	31.954
4 hr	1.997	69.862	0.070	0.349	1.787	39.716
5 hr	1.817	63.655	0.064	0.318	2.106	46.789

Table no. 10- In vitro drug release for Batch C

time	absorbance	concentration 5 ml (µg/ml)	concentration 5 ml (mg/ml)	concentration in 25 ml (mg/ml)	Cumulative concentration	% CDR
0.5 hr	1.084	38.379	0.038	0.192	0.192	4.264
1 hr	1.428	50.241	0.050	0.251	0.443	9.847
2 hr	2.067	72.276	0.072	0.361	0.804	17.877
3 hr	2.171	75.862	0.076	0.379	1.184	26.307
4 hr	1.982	69.345	0.069	0.347	1.531	34.011
5 hr	1.381	48.621	0.049	0.243	1.774	39.414

Table no. 11- In vitro drug release for Batch D

Figure 4 cumulative % drug release for batch C

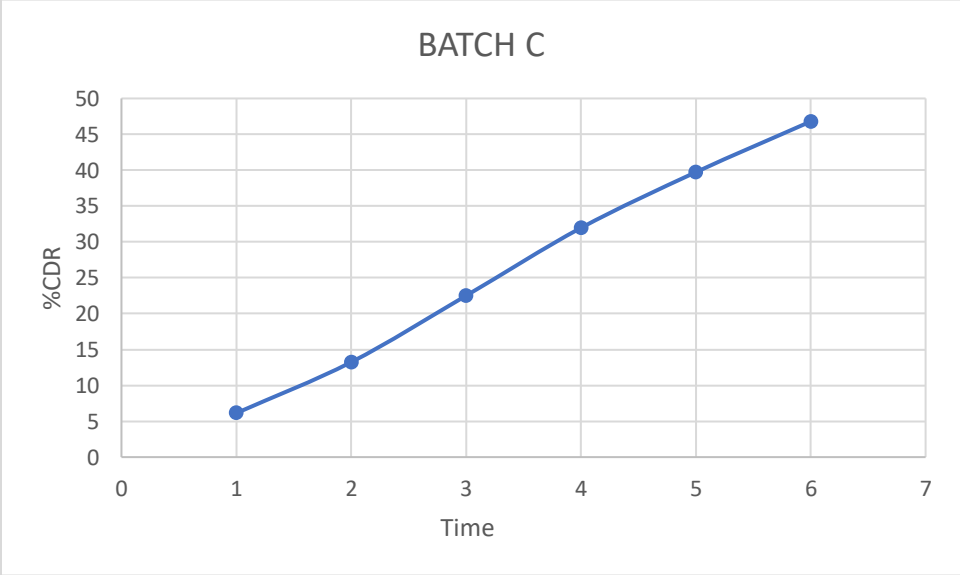


Figure 5 cumulative % drug release for batch D

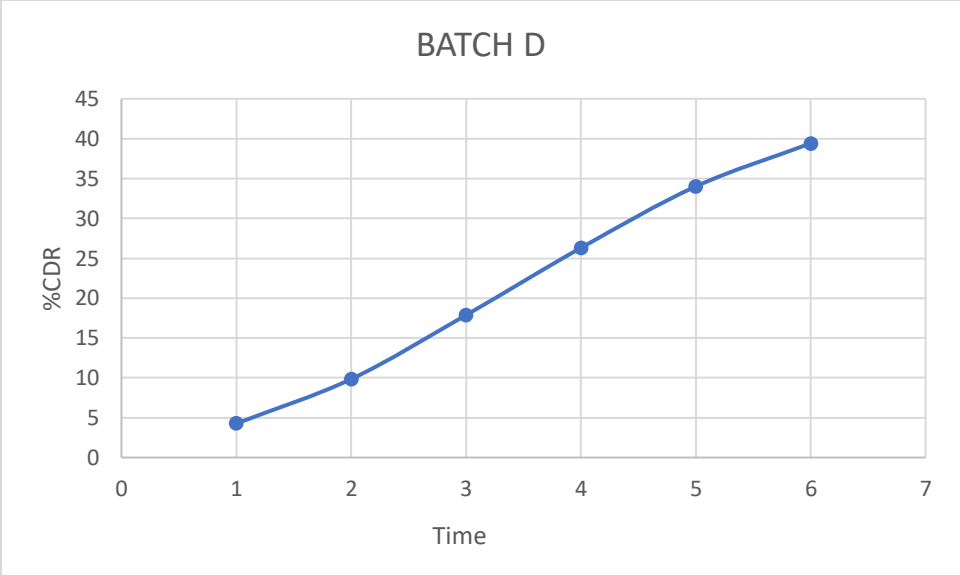


Figure 6- The cumulative % drug release of both batch A and B.

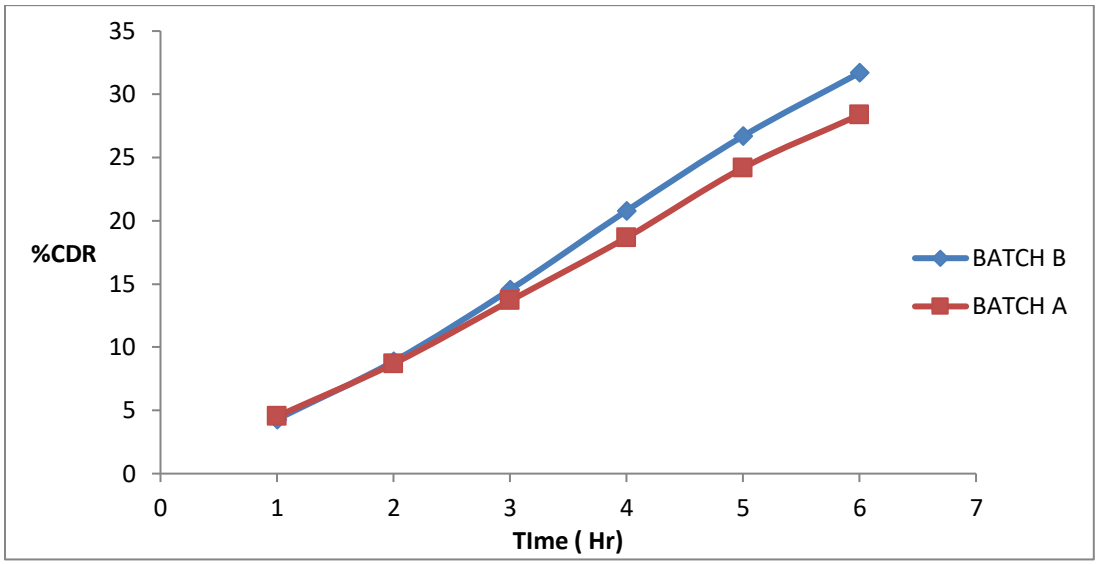


Figure 6

Figure 7- The cumulative % drug release of both batch C and D

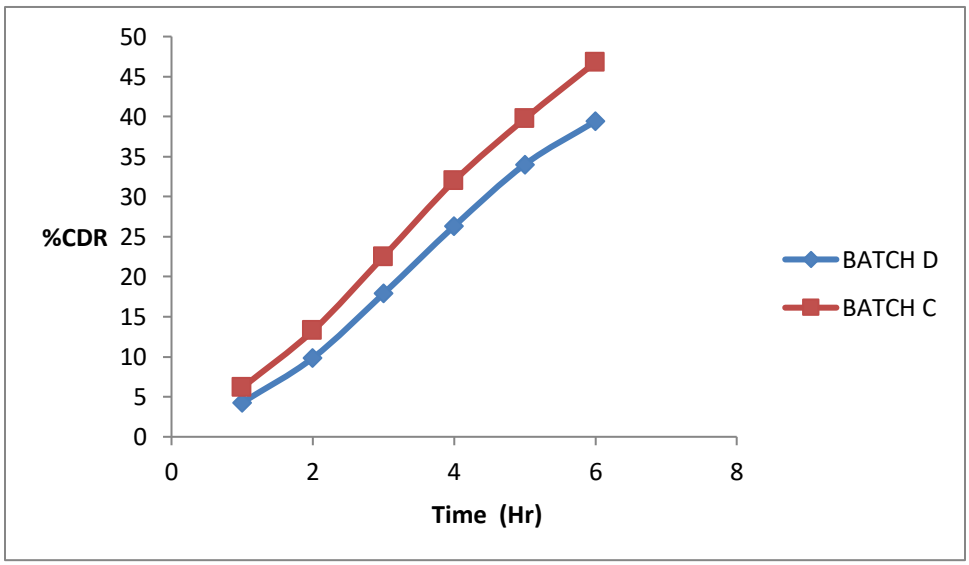


Figure 7

Conclusion It can be inferred from the performed evaluation tests that the drug release of batch B that is 31.690% as compared to batch A which showed the drug release of 28.366% . Similarly, in case of the gels the drug release of batch C that is 46.789% as

compared to that of batch D that is 39.414%. Thus it can be inferred from the following that increase in the concentration of gelling agent like Carbopol will reduce the drug release whereas in cream containing stearic acid better drug release was obtained than the one containing bees wax. Thus the most optimized batch for creams was batch B and for gels it was batch C. Further both these optimized batches could be validated for its rheological properties, viscosity and spreadability.

References

- Bjarnason I, Gastrointestinal safety of NSAIDs and over-the-counter analgesics. Int J Clin Pract Suppl. 2013;178:37–42. doi:10.1111/ijcp.
- Franz TJ. Percutaneous absorption on the relevance of in vitro data. J Invest Dermatol. 1975;64(3):190–195.
- Brown MB, Martin GP, Jones SA, et al. Dermal and transdermal drug delivery systems: current and future prospects. Drug Deliv 2006;13:175-87
- Barkin R, Berckerman M, Blum S, et al. Should nonsteroidal anti-inflammatory drugs (NSAIDs) be prescribed to the older adult? Drugs Aging 2010;27:775-89
- Sera UV, Ramana MV. In vitro skin absorption and drug release – a comparison of four commercial hydrophilic gel preparations for topical use. The Indian Pharmacist. 2006, 73 356-60.
- A. C. Sintov and S. Botner, "Transdermal drug delivery using microemulsion and aqueous systems: influence of skin storage conditions on the in vitro permeability of diclofenac from aqueous vehicle systems," *International Journal of Pharmaceutics*, vol. 311, no. 1-2, pp. 55–62, 2006

- Barry B.,Transdermal Drug Delivery. In: Aulton ME, Pharmaceutics. The science of dosage form design. 2nd ed. Churchill, Livingstone, 2002; 499-543.
- Swamy N.G.N., Mazhar P., Zaheer A., Formulation and evaluation of Diclofenac sodium gels using Sodium carboxymethyl Hydroxypropyl Guar and Hydroxypropyl methylcellulose. Indian J. Pharm. Educ. Res. 2010; 44 (4): 310-314.
- Diclofenac.com "The reference site for diclofenac" Website. http://www.diclofenac.com /index.html. Accessed on 28 May 2011.
- Arora P, Mukherjee B; Design, development, physicochemical and in-vitro and in-vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. J Pharm Sci. 2002; 91:2076-2089.
- Mohamed M I; Optimization of Chlorphenesin Emulgel Formulation" AAPS J. 2004; 6(3):26.
- "Principle of Skin Theraphy" Website. http://www.dermweb.com/ therapy/ common.htm. Accessed on 28 May 2011.
- Amnon C Sintov and Shafir Botner; Transdermal drug delivery using microemulsion and aqueous systems: Influence of skin storage conditions on the in vitro permeability of diclofenac from aqueous vehicle systems. International Journal of Pharmaceutics. 2006; 311:(1-2)55-62.
- Pharmacopeial Forum, The journal of standards development and official Compendia revision, 2007; 33:6.

BPharm Thesis V4

ORIGINALITY REPORT

6%	2%	0%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Institute of Technology, Nirma University Student Paper	3%
2	Submitted to Amrita Vishwa Vidyapeetham Student Paper	1%
3	www.labautopedia.org Internet Source	1%
4	hdl.handle.net Internet Source	1%
5	Submitted to The Robert Gordon University Student Paper	<1%
6	etd.lsu.edu Internet Source	<1%
7	Péter Sipos. "Influence of preparation conditions on the properties of Eudragit microspheres produced by a double emulsion method", Drug Development Research, 01/2005 Publication	<1%

Submitted to University of Keele

8	Student Paper	<1%

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	Off		