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RESEARCH ARTICLE

Formulation and Evaluation of Transdermal Drug Delivery System of an Anti-Diabetic Drug

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ABSTRACT

The main objective of the present research work was to formulate and evaluate a controlled release matrix type transdermal patch of Metformin hydrochloride. Transdermal drug delivery can be efficiently used for the active agents which cause severe gastric irritation and undergo rapid first pass metabolism, hence the transdermal patches of Metformin hydrochloride were prepared by using a combination of a hydrophilic polymer HPMC K_4M, hydrophobic polymer Ethyl cellulose and natural polymer chitosan along with propylene glycol as a plasticizer and Tween 80 as a permeation enhancer. The drug-excipients compatibility studies were performed by *FT-IR*. Nine different formulations were prepared using single polymer as well as combination of two polymers in 1:2 ratio. Out of the nine formulations, F8 and F9 did not form intact patches. The prepared formulations F1 to F7 were evaluated for weight variation, thickness, folding endurance, % flatness, moisture content, moisture uptake, drug content and *in vitro* diffusion studies. *In vitro* drug release test was carried for 24hours and formulation F6 showed 92.38% drug release at the end of 24hours. Formulation F6 was thus selected as the best formulation depending on the drug release and other properties. Release kinetic studies revealed that the drug release from F6 followed zero order kinetics and Korsmeyer-Peppas model with release exponent value n=1.017, which shows that release pattern of patches follows super case II transport. The patch exhibited negligible skin irritation as well as good *in vitro* drug permeation rate across the rat skin. Stability study was conducted for F6 formulation as per ICH guidelines and showed no significant changes during study. From the study, it can be concluded that the prepared matrix type transdermal patches of Metformin hydrochloride might be a potential formulation for the management of patients with type 2 Diabetes mellitus.

KEYWORDS

Metformin Hydrochloride, Diabetes Mellitus, Matrix Type Transdermal Patch, *In Vitro* Drug Release, Skin Irritation, *In Vitro* Drug Permeation

INTRODUCTION

Current efforts in the area of drug delivery include the development of targeted delivery in which the drug is only active in the target area of the body (for example, in the cancerous tissues) and sustained release formulations in which the drug is released over a period of time in a controlled manner from a formulation. In order to achieve efficient targeted delivery, the designed system must avoid the host's defence mechanisms and circulate to its intended site of action.[1]

Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which,

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when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation.[2] Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of the intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time. The skin acts as a formidable barrier to the penetration of drugs and other chemicals. It does have certain advantages which make it an alternative route for systemic delivery of drugs. Recently there has been an increasing awareness that the benefits of intravenous drug infusion can be closely duplicated, without its potential hazards by continuous transdermal drug administration through intact skin.

Diabetes mellitus is defined by the American Diabetes Association Expert Committee in their 1997 recommendations as "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidney, nerves, heart and blood vessels." Thus, diabetes covers a wide range of heterogeneous diseases. Several groups of drugs, mostly given by mouth, are effective in Type 2 Diabetes mellitus.

Judicious choice of drug is critical in the successful development of a transdermal product. The important drug properties that affect its diffusion from device as well as across the skin include molecular weight, solubility, physical properties and melting point. Majority of drugs will not penetrate the skin at the rates sufficiently high for therapeutic efficacy. The permeation can be improved by the addition of permeation enhancers like dimethyl Sulfoxide, dimethyl formamide, propylene glycol, etc into the system.

MATERIAL AND METHODS

Metformin hydrochloride obtained from S D Fine-Chem Limited, Mumbai, India. Hydroxypropyl methylcellulose obtained from LobaChemice, Mumbai, India. Ethylcellulose obtained from Rolex Chemical Industries, Mumbai, India. Chitosan gifted by Central Cochin Fisheries Ltd, Cochin, India. Propylene glycol, Tween 80, Ethanol and Dichloromethane were from S D Fine-Chem Limited, Mumbai, India. All other chemicals and reagents used in the study were of analytical grade.

Preparation of Transdermal Patches

The matrix type transdermal patches containing Metformin HCl were prepared by solvent evaporation technique using different proportions of polymers like HPMC K_4M, Ethyl cellulose and Chitosan. The polymers were dissolved in suitable solvents and mixed well by using a magnetic stirrer. Metformin HCl was slowly added to the polymer solution and mixed thoroughly to obtain a uniform solution. Propylene glycol and Tween 80 was then added to this solution. The drug polymeric solution was poured into petriplate placed on a level, hard rigid surface. Solvent evaporation was controlled by covering with placement of funnel in its inverted position. After 24hrs the patches were removed and kept in dessicators until they were used for further study. Nine such formulations were prepared using single polymer and combination of two different polymers in the ratio 1:2. The formulation chart is given in Table 1.

Evaluation of Transdermal Patches

Drug Polymer Interaction Study

The physicochemical compatibility between Metformin HCl and polymers used in the films was studied by using Fourier transform-infrared (FT-IR, Shimadzu Co., Japan) spectroscopy. The pellatization was done by the KBr pellet method. The FT-IR spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Metformin HCl and physical mixtures of Metformin HCl with polymers were compared.

Weight Variation Study[3,4]

Weight variation was studied by individually weighing 3 randomly selected patches from each formulation.

Table 1: Formulation Chart of Transdermal Patches

Formulation	Metformin Hydrochloride (mg)	Polymer ratio HPMC:EC:Chitosan	Propylene glycol (ml)	Tween80 (ml)	Solvent ratio Ethanol: DCM
F1	20	1:0:0	0.6	0.1	1:1
F2	20	0:1:0	0.6	0.1	1:1
F3	20	0:0:1	0.6	0.1	1:1
F4	20	1:2:0	0.6	0.1	1:1
F5	20	2:1:0	0.6	0.1	1:1
F6	20	2:0:1	0.6	0.1	1:1
F7	20	1:0:2	0.6	0.1	1:1
F8	20	0:2:1	0.6	0.1	1:1
F9	20	0:1:2	0.6	0.1	1:1

Their average weight was calculated and recorded.

Folding Endurance[3,5]

The folding endurance was measured manually. The patches were repeatedly folded at the same place till it broke. The number of times the patches could be folded at the same place without breaking gives the accurate value of folding endurance.

Uniformity of Thickness[3]

The uniformity of thickness of transdermal patches was measured by a micrometer with least count of 0-0.1 mm. The thickness of the patch was measured at three different points and the average of five readings with standard deviation was calculated.

Percent Flatness Study[3]

The preparing strips were cut out from each transdermal patch, one from the centre and two from the either side. The length of each strip was measured and the variation in the length because of non-uniform in flatness was measured by determining the % of constriction, considering 0% constriction is equivalent to 100% flatness.

$$\% \text{ of constriction} = (I_1\text{-}I_2)/ I_2$$

Where, I_1 = initial length of each strip and

I_2 = final length of each strip

Moisture Content[3,5,6]

The prepared patches were marked, then individually weighed and kept in a vacuum desiccator containing anhydrous calcium chloride at room temperature for 24hrs. The patches were individually weighed until they showed a constant weight. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

$$\% \text{ of moisture content} = (X\text{-}Y/Y) * 100$$

Where, X = initial weight, Y = final weight

Moisture Uptake[3,5,6]

The weighed patches were kept for drying in vacuum desiccator at normal room temperature for 24hrs upto a constant weight and then

exposed to 84% relative humidity (saturated solution of potassium chloride).

$$\% \text{ of moisture uptake} = (Y-X/X) * 100$$

Where, X = initial weight, Y = final weight

Drug Content Study[3,5]

Drug content study was carried out using pH 7.4 phosphate buffer. Patches of 1.5cm^2 were taken individually, crushed using mortar and pestle and taken in 100ml volumetric flask. With the help of a teflon coated magnetic bead the medium was stirred for 5hrs. The contents were filtered using Whatmann filter paper and the filtrate was examined for the drug content at 233nm respectively.

In Vitro Diffusion Study[3,5]

The *in vitro* drug release profile of Metformin HCl from the prepared matrix patch was studied using a Franz diffusion cell. The receptor compartment of the diffusion cell has a capacity of 100ml. The dialysis membrane previously soaked for 24hrs in pH 7.4 phosphate buffer was mounted between the donor and receptor compartment of the diffusion cell. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The total setup was placed on a thermostatically controlled magnetic stirrer set at 37 ± 2°C. The content of the diffusion cell was stirred continuously at a constant speed (500 rpm). Samples were withdrawn at predetermined time intervals and replaced with same amount of buffer to maintain the sink condition. The samples were analyzed for drug content using UV spectrophotometer at 233nm.

In Vitro skin Permeation Study[3,7]

Skin was excised from the experimental rat, whose hair has been previously removed. Adhering fat and other visceral tissue were removed carefully. Franz diffusion cells are used to assess *in vitro* drug permeation of metformin hydrochloride from the prepared transdermal patch. The receptor compartment was kept at 37^{0}C. The receptor fluid was selected as pH 7.4 phosphate buffer and it was stirred continuously with a magnetic stirrer at 500rpm. The formulation was placed in the donor compartment. Permeation experiments are to be carried out until 24hrs after application. Samples are taken from the receiver compartment at scheduled time intervals and replaced with same volume of fresh receptor fluid. The samples were then analysed for drug content using UV spectrophotometer at 233nm. The results are shown in Figure 6.

Kinetics of Drug Release

The suitability of several equations to identify the mechanisms for the release of drug was tested with respect to the release data. The drug release data of the *in vitro* dissolution study was analysed with various kinetic equations like zero order (% release v/s time), first order (Log % retained v/s time), Higuchi model (% release v/s square root time) and Korsmeyerpeppas equation (Log % release v/s Log time). Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots and are shown in Table-4. The value of 'n' gives an indication of the release mechanism; when n=1, the release rate is independent of time (case II transport), n= 0.5 for Fickian diffusion, 0.5<n<1.0 for anomalous (non-Fickian) diffusion and lastly, n>1.0 for super case II transport.

Stability Studies[8]

The accelerated stability test of optimized formulation was carried out as per ICH guidelines i.e. at 40±2°C/ 75±5% RH in humidity chamber for 3 months. After each month the samples were analyzed for any changes in weight variation, folding endurance, thickness, % flatness, moisture content, moisture uptake, drug content and drug release. FT-IR of the optimized formulation was done at the end of stability period to check the compatibility of the drug in the formulation.

Primary Skin Irritation Study[9,10]

Skin irritation test was done on experimental rats to evaluate the irritation potential of the prepared metformin hydrochloride transdermal patch. The optimized transdermal formulation was evaluated for skin irritation studies on 12 healthy rats.

Albino rats of male sex, weighing 150 to 200g each were used in this study (n=6 in each group). The back of the rats were shaved 24hrs prior to the formulation application. The rats were divided into 2 groups. A control patch (without any drug, group I) and an experimental patch (group II) were fixed firmly (dorsal side) to the shaved skin of the rats by means of adhesive tape USP. The skin surface was observed for any visible change such as erythema, redness after 24, 48 & 72hrs of the formulation application. The mean edemal and erythemal scores are recorded depending on the degree of erythema as reported by Draize method.

RESULTS AND DISCUSSION

Nine formulations (F1 to F9) of matrix type transdermal patches of Metformin hydrochloride were prepared using polymers in different ratios as shown in the formulation table.

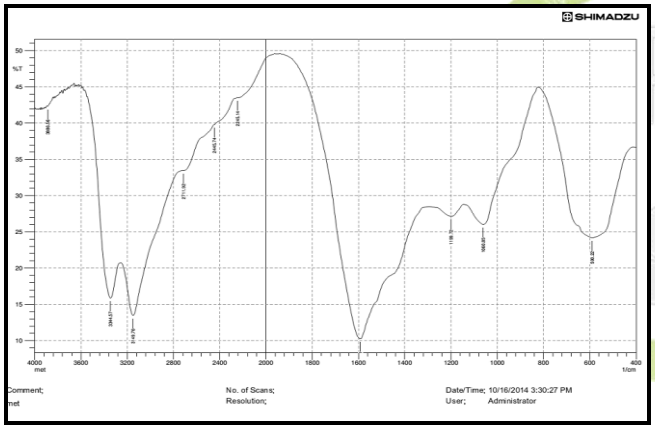

Figure 1: FT-IR Graph of the Pure Drug Metformin hydrochloride

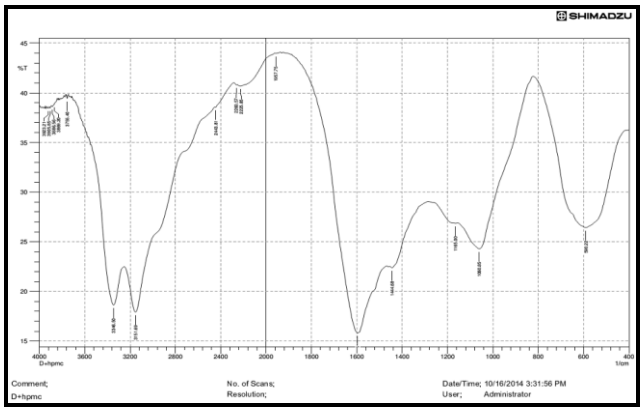

Figure 2: FT-IR Graph of Metformin hydrochloride and HPMC K4M

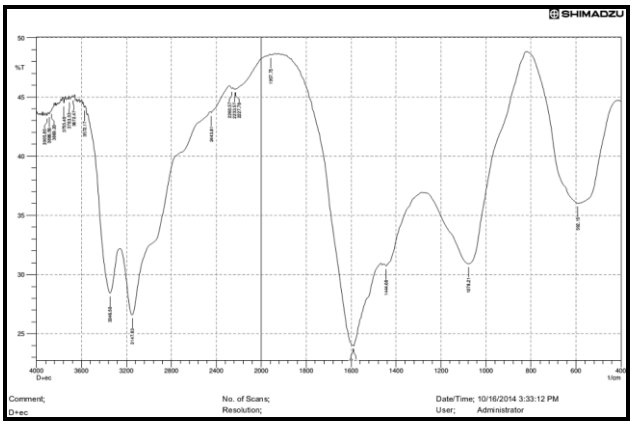

Figure 3: FT-IR Graph of Metformin hydrochloride and Ethyl cellulose

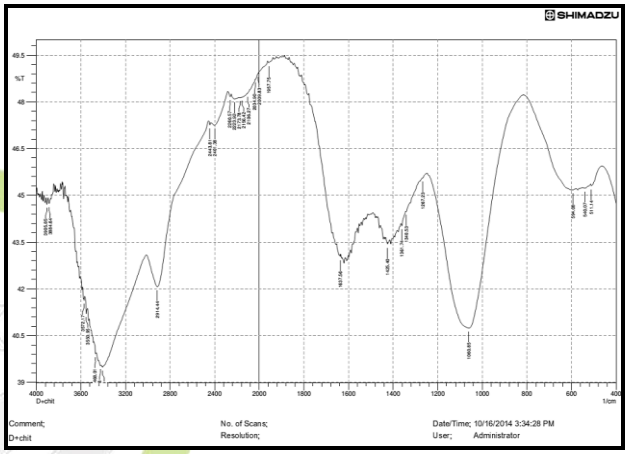

Figure 4: FT-IR Graph of Metformin hydrochloride and Chitosan

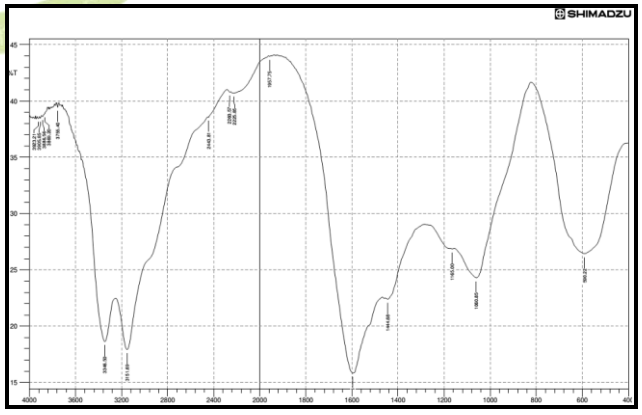

Figure 5: FT-IR Graph of F6 after Stability Study

FT-IR study was done to ensure the compatibility of the drug- Metformin hydrochloride with the selected polymers and excipients. The obtained FT-IR graphs are shown in figure 1 to 5. Pre-formulation study was done before the preparation of the patches.

Transdermal patches of Metformin hydrochloride were prepared by solvent evaporation technique using single and combination of the selected polymers. The prepared patches also contained plasticizer to enhance the smoothness and elasticity of the patches. Permeation enhancer was added to the patches to enhance the permeation of the drug through the skin. Nine such formulations were prepared. Out of the nine formulations mentioned in the formulation chart, seven formulations (F1-F7) successfully gave good patches and the remaining two formulations (F8 and F9) did not form intact patches. The prepared patches were stored in desiccators for further studies.

After the patches were prepared, they were subjected to the general test for patches like weight variation, folding endurance, film thickness, % flatness study, moisture content, moisture uptake, drug content, *in vitro* drug release and stability study. Some special tests like skin irritation and in vitro skin permeation studies were also done.

The cumulative % drug release of metformin hydrochloride patches during the *in vitro* drug release study of F1 to F7 was found to be 80.64% to 92.38% after 24hrs. F6 with a release of 92.38% was then selected as the best formulation for further studies. The skin diffusion of the prepared best formulation was confirmed by skin permeation study using rat skin. The F6 patch exhibited negligible skin irritation on rats.

The selected formulation (F6) was subjected to stability test at 40±2°C/ 75±5% relative humidity for 3 months. The results as shown in table-5 indicate that there was no statistically significant difference between the initial values and the values obtained during stability studies.

Table 2: Physicochemical Parameters of Transdermal Patches

Formulation	Thickness* (µm)	Weight* (mg)	Folding endurance*	% Flatness
F1	220 ± 0.01	47.43 ± 2.6	51 ± 02	99
F2	202 ± 0.21	42.73 ± 1.9	10 ± 03	100
F3	210 ± 0.02	45.03 ± 3.2	150 ± 05	99
F4	212 ± 1.21	43.23 ± 2.2	85 ± 04	100
F5	208 ± 1.83	49.8 ± 4.2	83 ± 05	100
F6	200 ± 0.03	41.93 ± 1.8	41 ± 02	100
F7	210 ± 0.02	50.63 ± 3.2	54 ± 03	98

*All data are presented in Average ± SD, n=3

Table 3: Evaluations of Transdermal Patches

Formulation	% Moisture Content*	% Moisture Uptake*	Percentage Drug Content	Cumulative % CDR
F1	3.773 ± 0.055	5.724 ± 0.132	89.95	87.30
F2	0.942 ± 0.62	0.152 ± 0.21	87.57	80.64
F3	2.44 ± 0.76	22.03 ± 0.26	82.76	89.20
F4	0.923 ± 0.45	0.084 ± 0.26	92.53	82.93
F5	1.323 ± 0.32	1.021 ± 0.42	92.23	91.87
F6	1.210 ± 0.59	1.198 ± 1.076	91.15	92.38
F7	1.011 ± 0.68	0.982 ± 0.854	91.55	84.78

*All data are presented in Average ± SD, n=3

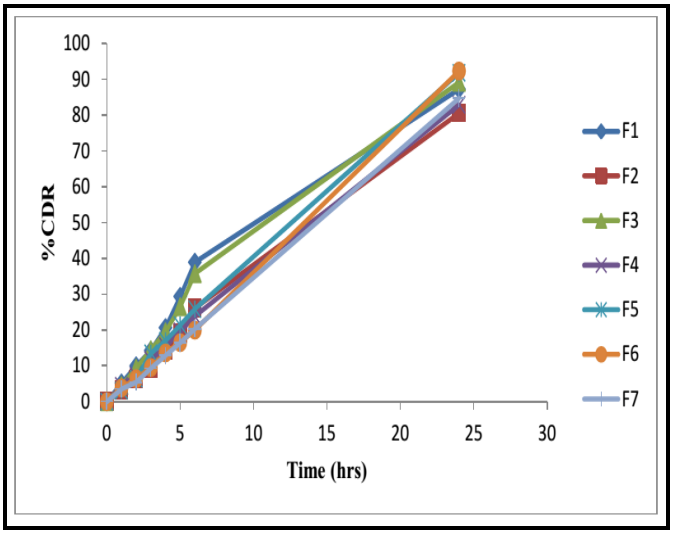

Figure 6: *In Vitro* Release Profile

Table 4: Correlation Coefficient of F6 in Various Kinetic Models

Release kinetic model	**F6 (R^2 value)**
Zero order	0.998
First order	0.968
Higuchi model	0.952
Korsmeyer-Peppas model	0.994

Table 5: Changes in Various Parameters during Stability Study Period

Parameters	**Condition (40±2°C/75±5%RH)**		
	30 days	**60 days**	**90 days**
Weight uniformity	42.93 ± 0.41	43.81 ± 0.02	44.41 ± 0.06
Folding endurance	43 ± 03	45 ± 02	42 ± 01
% Drug content	91.88	92.76	91.91
% Moisture content	1.36 ± 0.37	1.45 ± 0.72	1.65 ± 0.06

CONCLUSION

In the present study, an attempt was made to formulate the transdermal patches of metformin hydrochloride that solves the drawbacks as well as prevent the side effects and risk factors associated with oral dose of metformin hydrochloride in the treatment of type 2 Diabetes mellitus. The diffusion data of F6 was found best fitted in zero order and Korsmeyer-Peppas model (n=1.017) showing that the drug release is independent of drug concentration and the drug release follows super case II transport i.e. erosion of the polymeric chain. The present study proved that the prepared transdermal patches of metformin hydrochloride exhibited good controlled release characteristics and were found suitable for the treatment of type 2 Diabetes mellitus.

In conclusion, the prepared metformin hydrochloride transdermal patches might be a potential formulation for the management of patients with type 2 Diabetes mellitus.

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REFERENCES

1. Wade A. and Weller P. J. (1994).Handbook of Pharmaceutical Excipients. 2nd ed. Washington D.C: *American Pharmaceutical Publishing Association*, 362-66.
2. Chein Y. W. (1992). Novel Drug Delivery System. 2nd ed. New York: Marcel Dekker; 301-42.
3. Arijit, D., Sibaji, G., Biplab, K. D., & Sudip, D. (2010). A novel technique for treating the type-ll diabetes by transdermal patches prepared by using multiple polymer complexes. *International Journal of Pharmaceutical Research and Development*, *9*, 195-204.
4. Saxena, M., Mutalik, S., & Reddy, M. S. (2006). Formulation and evaluation of transdermal patches of metoclopramide

hydrochloride. *Indian Drugs-Bombay*, *43*(9), 740.

5. Gupta, J. R. D., Irchhiaya, R., Garud, N., Tripathi, P., Dubey, P., & Patel, J. R. (2009). Formulation and evaluation of matrix type transdermal patches of Glibenclamide. *International Journal of Pharmaceutical Sciences and Drug Research*, *1*(1), 46-50.
6. Gupta, R., Bajpai, M., & Bhattacharya, A. (2008). Formulation and in vitro evaluation of transdermal drug delivery system of tizanidine hydrochloride. *Journal of Pharmacy Research*, *7*(4), 208-213.
7. Pachisia, N., & Agrawal, S. S. (2012). Formulation, development and evaluation of transdermal drug delivery system of glimepiride. *International Journal of Pharmacy and Pharmaceutical Sciences*, *2*, 1-8.
8. Gosh T., Jasti B. (2005). Theory and Practice of contemporary pharmaceutics. London: CRC press, 217-48.
9. Baek, J. S., Lim, J. H., Kang, J. S., Shin, S. C., Jung, S. H., & Cho, C. W. (2013). Enhanced transdermal drug delivery of zaltoprofen using a novel formulation. *International Journal of Pharmaceutics*, *453*(2), 358-362.
10. Draize, J. H, Woodard, G., Calvery H. O. (1944). *Journal of Pharmacology and Experimental Therapeutics*, 82, 377–390.

