Formulation and Evaluation of Transdermal patches of Diclofenac Sodium and Tizanidine Hydrochloride

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Abstract

Diclofenac Sodium an NSAID, used for the treatment of rheumatoid arthritis and osteoarthritis. Tizanidine is a Clonidine congener.It inhibits polysynaptic reflexes; reduces muscle tone and frequency of muscle spasms without reducing muscle strength. An improved Diclofenac Sodium-Tizanidine Hydrochloride formulation with a high degree of permeation could be useful in treatment of locally inflamed skin, inflammatory and painful states of supporting structures of the body.The trandermal Patches were formulated using varying ratio of hyrophillic polymers, penetration enhancers and plasticizers Dimethyl sulfoxide and Polyethylene glycol 400 dissolved in methanol-water by solvent casting method. The Physiochemical properties of patches were evaluated. Combination strategy of drugs and permeation enhancers showed convincing results with significant improvement in the transportation of Diclofenac Sodium-Tizanidine Hydrochloride carried out by permeation studies using Franz diffusion cell on rat abdominal skin. Tween 80 (5%w/w) and span 80 (5%w/w) were identified as key enhancers that could improve the transport of Diclofenac Sodium-Tizanidine Hydrochloride across the skin. The drug release kinetics followed zero order kinetics and data from koresmeyer-peppas model indicates that the release mechanism follow fickian diffusion. The percent of drug permeated in 12 h was found to be maximum 99.8± 0.01 and 98.98± 0.01 % from formulations FA2 and FA8 respectively. Hence the transdermal patch would prove to be a promising formulation.

Key Words-Transdermal Patch, Physiochemical Properties, Diclofenac Sodium, Tizanidine Hydrocloride,Franz Diffusion cell

Introduction

Diclofenac is a NSAID having poor oral bioavailability of 50-60%. It is available in oral solid dosage form which is thought to be frequently administered 2-3 times daily leading to ulceration and bleeding of stomach.[1]Tizanidine is a type of central analgesic (acts on the central nerves in the brain and the spinal cord to relieve muscle tonicity). This drug is used to alleviate discomfort from shoulder stiffness, back problems, frozen shoulder, tension, headache and other problems.[2] Transdermal delivery route could be extremely useful for diclofenac, as it would lessen the need of specialized care, avoids first pass effect and gastro intestinal disturbances when administered for prolong duration. [3]The aim of the research work was to enhance the transdermal permeation of Diclofenac-Tizanidine by optimizing the formulation with suitable penetration enhancers via skin. Transdermal delivery of combination drugs can also enhance the regional delivery of Diclofenac and Tizanidine for patients suffering for pain and spans as in case of musculoskeletal spasm and are also approved for the treatment of spasticity thereby relieve the pain and inflammation.

Literature Survey-

Katti *et al.* (2017) formulated and developed transdermal patch of Tizanidine Hydrochloride which will overcome the limitation of bioavailability. In this study transdermal patches were prepared by solvent-casting method using hydrophilic polymer HPMC E-5 LV, chitosan, *Moringa oleifera* gum and Propylene Glycol as plasticizer.[4] **Pravallika *et al.* (2014)** developed an isocratic, reversed phase-liquid-chromatographic method for the quantitative determination of Tizanidine and Diclofenac Sodium combined-tablet dosage form.[5] **Bhargava *et al.*, (2015)**, compared the analgesic effects of Diclofenac transdermal patch (100mg)-Nupatch and Diclofenac intramuscular injection (75mg) in the management of post operative pain, to observe the efficacy, duration, quality of analgesic effect on visual analogue scale and to observe any adverse effects of Diclofenac patch and Diclofenac injection in short term use.[6] **Guang yan *et al.*, (2014)** determine the extents of direct penetration across live rat skin from topical application of Diclofenac and its ester prodrug. Diclofenac and its prodrugs were formulated into patches with different pressure sensitive adhesives. In vitro flux studies across the human epidermis and across hairless rat skin were conducted.[7]

Method -

Preparation of casting solutions

The casting solutions For PVA and PVP Polymeric formulations FA1 to FA10 (Prabhu *et al*) were prepared by dissolving weighed quantities of various ratios of polymers in water. The drugs were dissolved in methanol and added to the above polymeric solution along with 10% Propylene Glycol 400 and 10% Dimethylsulfoxide as plasticizer separately, Tween 80(5% v/v) and Span 80(5% v/v) were add respectively and thoroughly mixed to form a homogeneous mixture by heating on heating mantle at 60°C. The volume 20 ml of this casting solution is poured into Petri plates and kept in the hot air open for drying.(Table 1)

Preparation of transdermal patches

Twenty milliliter of the casting solution was poured into petri plates and dried in hot air for 24 hours for solvent evaporation. The patches were removed by peeling and cut into square dimension of 2 cm × 2 cm (4 cm^2). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers.

Table 1-Preparation of transdermal patches using Propylene Glycol 400 & Tween 80

Code	*Formulation (Polymeric Ratio)*	*PVA (mg)*	*PVP (mg)*	*Drug (100 mg+2mg)*	*Plasticizer (Propylene Glycol 400)*	*Penetration Enhancers (Tween 80)*	*Methanol*	*Water*
FA1	10:0	1000	-	102	10% w/v	5% w/v	10	20
FA2	9:1	900	100	102	10% w/v	5% w/v	10	20
FA3	8:2	800	200	102	10% w/v	5% w/v	10	20
FA4	7:3	700	300	102	10% w/v	5% w/v	10	20
FA5	6:4	600	400	102	10% w/v	5% w/v	10	20

Table 2-Preparation of transdermal patches using Dimetylsulfoxide & Span 80

Code	*Formulation (Polymeric Ratio)*	*PVA (mg)*	*PVP (mg)*	*Drug (100 mg+2mg)*	*Plasticizer (DMSO)*	*Penetration Enhancers (Span 80)*	*Methanol*	*Water*
FA6	10:0	1000	-	102	10% w/v	5% w/v	10	20
FA7	9:1	900	100	102	10% w/v	5% w/v	10	20
FA8	8:2	800	200	102	10% w/v	5% w/v	10	20
FA9	7:3	700	300	102	10% w/v	5% w/v	10	20
FA10	6:4	600	400	102	10% w/v	5% w/v	10	20

Characterization Of Transdermal Patches

Physical appearance[8]

All the transdermal patches were visually inspected for color, clarity, flexibility, and smoothness.

Thickness of the films[9]

The thickness of the drug-loaded polymeric films were measured at three different places using a Vernier caliper and mean values were calculated.

Weight variation[10]

Weight variation was determined by weighing three patches individually, from each batch and the average weight was calculated.

Flatness [11]

The longitudinal strips were cut from the centre and both sides of each patch. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured as % constriction, and a 0% constriction was considered to be equivalent to 100% flatness.

Tensile strength[12]

Mechanical properties of the polymeric patches were determined by measuring their tensile strength. These mechanical properties were evaluated using Instron universal testing instrument (model F. 4026) with a 5 kg load cell. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3cm. During measurement, the strips were pulled by the top clamps at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two

mechanical properties, namely tensile strength and percentage elongation, were computed for the evaluation of the film.

- Tensile strength =Force required to break the film/Intial cross sectional area (mm^2)' similarly, Percentage Elongation = Increase in length/Original length × 100

Table. 3: Characterization of transdermal Patches for Physiochemical Parameters-I

Form .code	*Thickness (mm)*	*Weight Variation(g)*	*Folding Endurance*	*Moisture Content*	*Tensile Strength*	*Percentag Moisture uptake*	*Moisture Vapour Transmissionn*	*Percentage Elongation*
FA1	0.29±0.03	31.32.±1.154	125-134	1.05±0.13	3.66±1.18	3.57±0.25	5.87×10^{-3}	83.724±15
FA2	0.24±0.02	30.33±1.156	125-130	0.75±0.13	4.69±0.23	3.13±0.36	4.27×10^{-3}	238± 0.002
FA3	0.25±0.03	31.60±0.144	126-134	0.13±0.13	5.13±0.13	3.57±0.26	4.17×10^{-3}	271± 0.100
FA4	0.23±0.01	32.23±1.154	121-134	0.19±0.17	4.76±1.18	3.13±0.37	13.77×10^{-3}	191± 0.03
FA5	0.19±0.02	31.33±1.155	126-137	1.16±0.14	4.89±0.23	4.57±0.27	6.87×10^{-3}	238± 0.02
FA6	0.27±0.01	32.66±1.165	121-134	0.19±0.18	4.13±0.13	5.13±0.38	7.77×10^{-3}	193±0.02
FA7	0.26±0.03	32.37±1.154	125-134	0.16±0.15	3.76±1.18	5.57±0.28	12.87×10^{-3}	83.91±15
FA8	0.25±0.03	31.78±0.111	121-134	0.19±0.19	4.59±0.23	5.13±0.39	13.77×10^{-3}	84.72±15
FA9	0.22±0.02	32.43±1.152	124-136	0.16±0.16	5.23 ±0.13	5.57±0.29	12.87×10^{-3}	85.72±15
FA10	0.23±0.01	31.36±1.154	121-129	0.19±0.20	4.66±1.18	5.13±0.40	10.77×10^{-3}	190.7±15

Mean ± SD, n = 3

Swellability[13-16]

This test is performed to check the swellability of the patch due to presence of polymer. This test requires Petri plates and double distilled water, to see how much the patch would swell upon contact with water. The patches of 3.14 cm^2 are weighed and placed in a Petri plates containing 10 ml of double distilled water and are allowed to imbibe for specified time.Increase in weight of the patch is then determined at specific time intervals until a constant weight is observed. The degree of swelling (%S) =weight of Patch at time(t)-weight of Patch at time (t_0)/Weight of patch at time (t_0)×100

Surface pH[17-18]

Surface pH of the patches is described by Bottenberg *et al.* The patches are kept in 0.5 ml double distilled water and thus allowed to swell for 1hour. The surface pH is known by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute.

Drug content [19-22]

Transdermal system of specified area (2 cm^2) was cut into small pieces and taken into a 100 ml volumetric flask and 100 ml of phosphate buffer pH 7.4 was added , and kept for 24 hours with occasional shaking. Then, the suitable dilution was made with phosphate buffer of pH 7.4. Similarly, a blank was carried out using a drug-free patch. The solutions were filtered and the absorbance was measured at 276 nm for Diclofenac sodium and 320 nm for Tizanidine Hydrochloride.

Percentage moisture uptake[23]

The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium chloride. Finally, the films were weighed.Percent moisture uptake =[Final weight - Initial weight/Initial weight] × 100

Moisture content [24]

The prepared films were weighed individually and kept in a desiccator containing silica at room temperature for 24 hours. The films were weighed again and again until they showed a constant weight. The percent moisture=[Initial weight - Final weight/Final weight] x100

Water vapor transmission rate[25-27]

Conical flasks of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1 gm anhydrous calcium chloride was placed in each flask and the prepared transdermal patches of each formulation were fixed over the brim with the help of adhesive. The cells were accurately weighed and kept in closed desiccators containing saturated solution of potassium chloride to maintain a relative

humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hrs of storage. Water vapor transmission rate is expressed as the number of grams of moisture gained /h/cm2.

Table. 4: Characterization of transdermal Patches for Physiochemical Parameters-II

Form code	*Swellability*	*Surface pH*	*Drug Content*		*Permeability coefficient*	*Flux*
			DLC	*TZN*		
FA1	16.97± 0.43	5.5 ± 0.14	99.99±0.8	99.99±0.8	0.88	0.0788
FA2	18.32 ± 0.39	5.6 ± 0.14	99.95±0.9	99.95±0.9	1.669	0.1539
FA3	19.18 ± 0.58	5.7 ± 0.12	95.99±0.10	96.99±0.10	2.418	0.2168
FA4	22.42 ± 0.57	5.5 ± 0.13	94.99±0.11	98.99±0.11	2.3933	0.227
FA5	23.43 ± 0.49	5.8± 0.12	99.07±0.12	98.07±0.12	2.848	0.2063
FA6	28.63 ± 0.54	5.5 ± 0.14	99.85±0.13	99.85±0.13	2.56	0.2294
FA7	30.13 ± 0.55	5.6 ± 0.14	93.55±0.14	94.55±0.14	2.28	0.2091
FA8	32.87 ± 0.46	5.7 ± 0.14	95.59±0.15	94.59±0.15	2.48	0.1686
FA9	35.48 ± 0.45	5.6 ± 0.12	97.99±0.16	98.99±0.16	2.824	0.2449
FA10	16.97± 0.43	5.8 ± 0.13	95.99±0.17	98.99±0.17	2.813	0.298

Mean ± SD, n = 3

In Vitro Skin Permeation Studies[28-30]

Preparation of the skin for permeation studies

A healthy Wistar Albino rat was selected and anesthetized with the chloroform. The hair from the abdominal region was shaved carefully with a safety razor and further cleaned with wet cotton to remove extra hairs. The rat was sacrificed by the proper method and the hairless clean skin was excised carefully with the help of a surgical blade. The procured skin was then cleaned thoroughly with distilled water and stored in Ringer solution with proper aeration.

Procedure

In vitro permeation studies were performed on Franz diffusion cells with an effective sectional area of 3.14 cm2 and 15 ml of receiver chamber capacity. The rat abdominal skin was tightly secured between the donor and receptor compartments. The upper surface of the membrane was exposed to solution of the formulated films and covered with paraffin film. The receptor compartment was filled with isotonic phosphate buffer pH 7.4. The whole assembly was kept on a magnetic stirrer and solution in the receptor compartment was constantly and continuously stirred using a magnetic bead. The solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37±0.5°C. The 2 ml aliquots were withdrawal at different time intervals (0,2,4,8,10,12 hours) and analyzed the drug content by UV-Visible spectrophotometer (117 Systronics) at 305 nm. The receptor phase was replenished with an equal volume of phosphate buffer (37°C) at each sample withdrawal, the cumulative amount of drug permeated per square centimeter (µg/cm2) of patches were plotted against time.

Permeability Coefficient (P) [31]

Permeability coefficient is the velocity of drug passage through the membrane/skin in mcg/cm^2/hour. The permeability coefficient was calculated from the slope of the graph of percentage of drug transported vs. time as: P = Slope x Vd/S Where, Vd = volume of donor solution, S = surface area of tissue.

Flux (J)

Flux is defined as the amount of material flowing through a unit cross-sectional barrier in unit time. It is calculated by: Flux (J) = P x CD where ,CD = concentration of drug in donor solution, P = permeability coefficient.

TABLE.5 *In-vitro* Permeation Profiles Of Transdermal Patches Containing Both the Drugs with Penetration enhancers Propylene Glycol 400& Tween 80

Time (hrs)	*FA1(%)*	*FA2 (%)*	*FA3 (%)*	*FA4 (%)*	*FA5 (%)*
0	0	0	0	0	0

2	5.34 ± 0.01	6.81± 0.01	6.25± 0.01	5.35± 0.01	3.82± 0.01
4	17.4 ± 0.01	17.7± 0.01	18.2± 0.01	18.2± 0.01	16.2± 0.01
6	35.7 ± 0.02	35.2± 0.01	36.6± 0.01	30.8± 0.01	34.5± 0.01
8	67.6 ± 0.01	64.4± 0.01	66.3± 0.01	56.2± 0.01	50.4± 0.01
10	92.7 ± 0.02	86.2± 0.01	90.8± 0.01	78.5± 0.01	73.7± 0.01
12	99.6 ± 0.03	99.8± 0.01	99.3± 0.01	94.4± 0.01	97.3± 0.01

Mean ± SD, n = 3

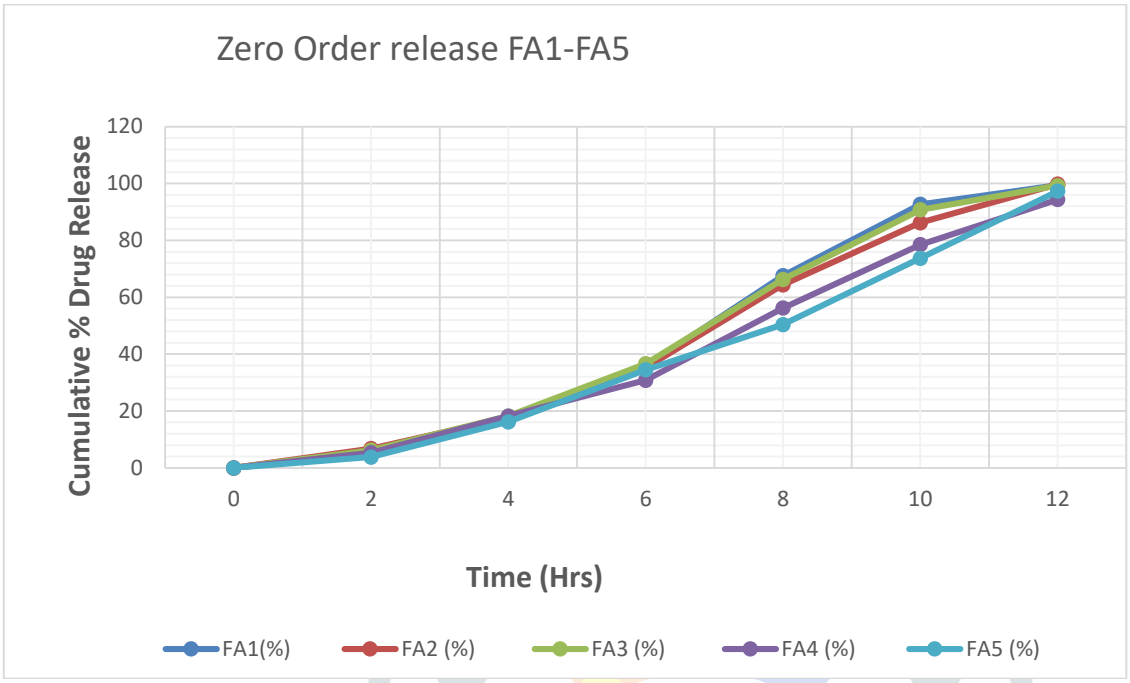

Fig.1 Zero order drug release for formulation FA1-FA5 (Propylene glycol-400& tween 800)

TABLE.6: *Invitro* Permeation Profiles Of Transdermal Patches Containing Both the Drugs with Penetration enhancers Dimetylsulfoxide & Span 80

Time (hrs)	*FA6 (%)*	*FA7 (%)*	*FA8 (%)*	*FA9(%)*	*FA10 (%)*
0	0	0	0	0	0
2	6.02± 0.01	6.22± 0.01	7.84± 0.01	6.65± 0.01	6.28± 0.01
4	17.52± 0.01	16.92± 0.01	20.56± 0.01	17.78± 0.01	20.3± 0.01
6	32.64± 0.01	36.24± 0.01	34.32± 0.01	28.16± 0.01	45.8± 0.01
8	64.34± 0.01	63.56± 0.01	67.71± 0.01	55.32± 0.01	64.4± 0.01
10	83.28± 0.01	81.86± 0.01	83.04± 0.01	76.12± 0.01	84.7± 0.01
12	98.21± 0.01	98.52± 0.01	98.98± 0.01	97.62± 0.01	98.11± 0.01

mean ± SD, n = 3

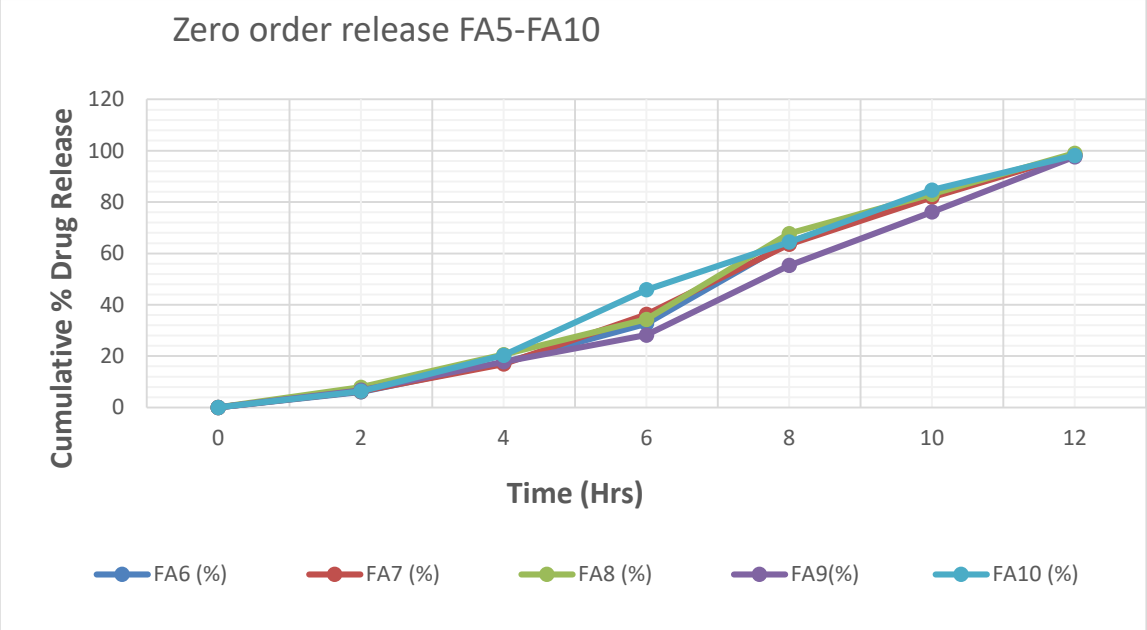

Fig.2-Zero Order drug release of formulation FA6-FA10 (Dimethyl Sulfoxide and Span 80)

Table 7: Analysis of First order drug release (Log Cumulative % drug unrelease vs. Time) for Formulations FA1-FA5

Time (hrs)	*FA1*	*FA2*	*FA3*	*FA4*	*FA5*
0	2± 0.02	2± 0.01	2± 0.01	2± 0.01	2± 0.01
2	1.9761± 0.03	1.9693± 0.03	1.9720± 0.02	1.9761± 0.01	1.9830± 0.01
4	1.9170± 0.01	1.9154± 0.04	1.9127± 0.03	1.9127± 0.07	1.9232± 0.05
6	1.8082± 0.04	1.8115± 0.03	1.8020± 0.02	1.8401± 0.05	1.8162± 0.02
8	1.5105± 0.05	1.5514± 0.05	1.5276± 0.01	1.6414± 0.02	1.6954± 0.03
10	0.8633± 0.06	1.1399± 0.01	0.9637± 0.05	1.3324± 0.01	1.4199± 0.01
12	0.2219± 0.01	0.6990± 0.03	0.1549± 0.01	0.7481± 0.01	0.4313± 0.01

Mean ± SD, n = 3

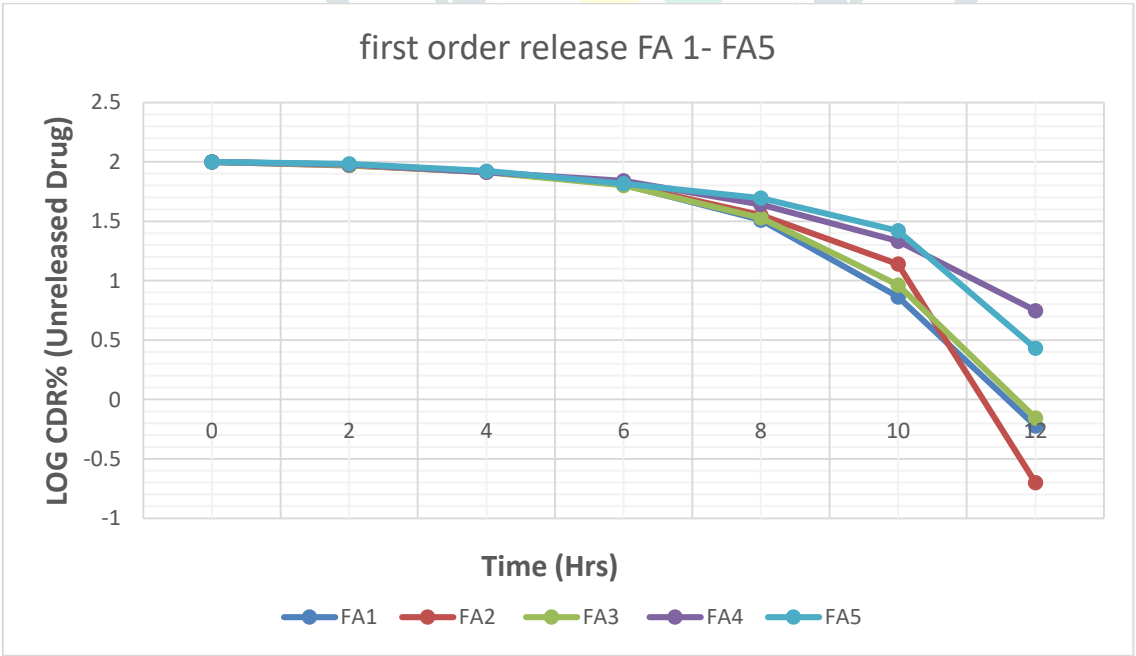

Fig.3: First order drug release for Formulations FA1-FA5

Table.8: Analysis of First order drug release (Log Cumulative % drug Unreleased vs. Time) for Formulations FA5-FA10

Time (hrs)	*FA6*	*FA7*	*FA8*	*FA9*	*FA10*
0	2± 0.01	2± 0.01	2± 0.01	2± 0.01	2± 0.01
2	1.9730± 0.01	1.9721± 0.01	1.9645± 0.06	1.9701± 0.01	1.9718± 0.01
4	1.9163± 0.02	1.9194± 0.02	1.9000± 0.01	1.9149± 0.01	1.9014± 0.01
6	1.8284± 0.02	1.8045± 0.01	1.8174± 0.05	1.8563± 0.01	1.7339± 0.01
8	1.5521± 0.05	1.5615± 0.07	1.5090± 0.05	1.6501± 0.01	1.5514± 0.01
10	1.2232± 0.01	1.2586± 0.01	1.2294± 0.01	1.3780± 0.01	1.1846± 0.01
12	0.2528± 0.01	0.1702± 0.01	0.0086± 0.01	0.3765± 0.01	0.2764± 0.01

Mean ± SD, n = 3

Fig.9:First order drug release for Formulations FA6-FA10

Table.9:Higuchi's diffusion model (Cumulative % drug release vs. Square root of time) For Formulations FA1-FA5

Time (Hrs)	*FA1*	*FA2*	*FA3*	*FA4*	*FA5*
0	0	0	0	0	0
1.41	5.34± 0.01	6.81± 0.01	6.25± 0.01	5.35± 0.01	3.82± 0.01
2	17.4± 0.01	17.7± 0.01	18.2± 0.01	18.2± 0.01	16.2± 0.01
2.45	35.7± 0.01	35.2± 0.01	36.6± 0.01	30.8± 0.01	34.5± 0.01
2.83	67.6± 0.01	64.4± 0.01	66.3± 0.01	56.2± 0.01	50.4± 0.01
3.16	92.7± 0.01	86.2± 0.01	90.8± 0.01	78.5± 0.01	73.7± 0.01
3.46	98.21± 0.01	98.52± 0.01	98.98± 0.01	97.62± 0.01	98.11± 0.01

Mean ± SD, n = 3

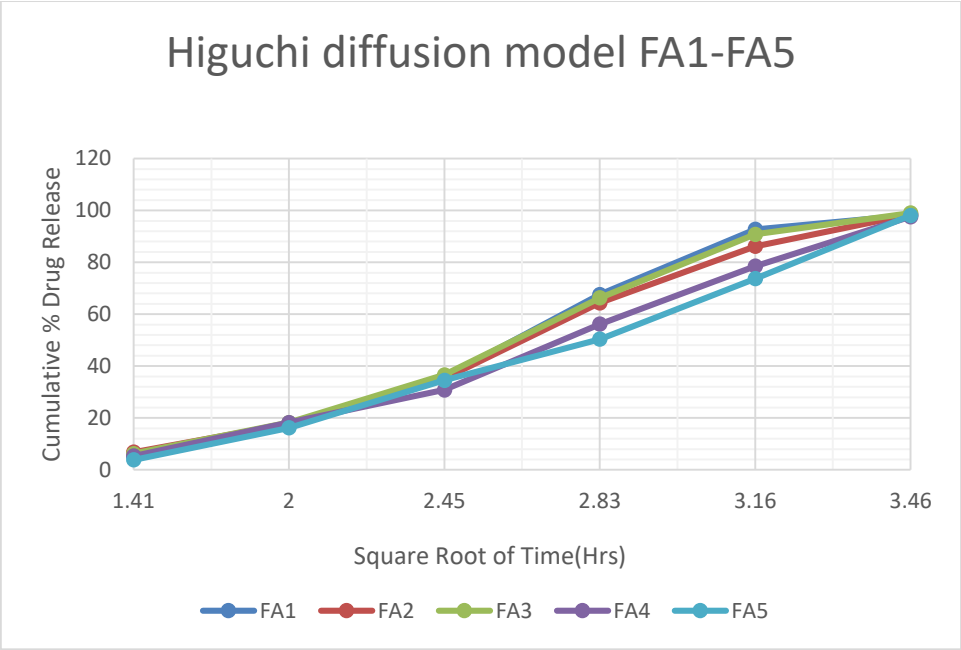

Fig.10:Higuchi's diffusion model For Formulations FA1-FA5

Table.10:Higuchi's diffusion model (Cumulative % drug release vs. Square root of time) For Formulations FA6-FA10

Time (Hrs)	*FA6*	*FA7*	*FA8*	*FA9*	*FA10*
1.41	6.02± 0.01	6.22± 0.01	7.84± 0.01	6.65± 0.01	6.28± 0.01
2	17.52± 0.01	16.92± 0.01	20.56± 0.01	17.78± 0.01	20.3± 0.01
2.45	32.64± 0.01	36.24± 0.01	34.32± 0.01	28.16± 0.01	45.8± 0.01
2.83	64.34± 0.01	63.56± 0.01	67.71± 0.01	55.32± 0.01	64.4± 0.01
3.16	83.28± 0.01	81.86± 0.01	83.04± 0.01	76.12± 0.01	84.7± 0.01
3.46	98.21± 0.01	98.52± 0.01	98.98± 0.01	97.62± 0.01	98.11± 0.01

Mean ± SD, n = 3

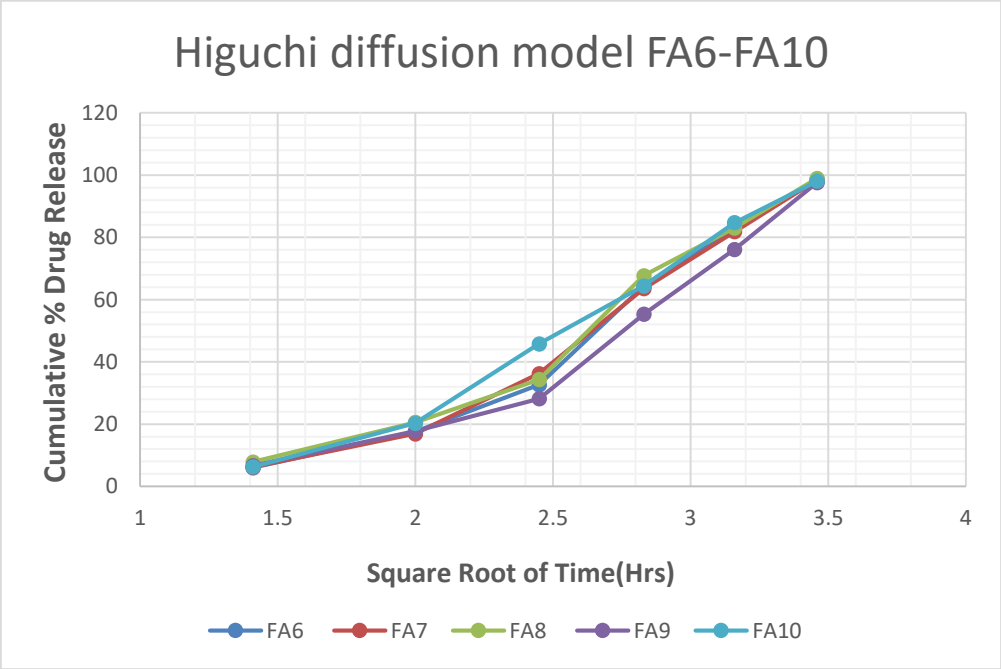

Fig.11:Higuchi's diffusion model For Formulations FA6-FA10

Table.11:Korsmeyer's release model (log Cumulative % drug release vs. log time) For Formulations FA1-FA5

Log time	FA1	FA2	FA3	FA4	FA5
0.301	0.728± 0.01	0.833± 0.01	0.796± 0.01	0.728± 0.01	0.582± 0.01

0.602	1.241± 0.01	1.248± 0.01	1.26± 0.01	1.26± 0.01	1.21± 0.01
0.778	1.553± 0.01	1.547± 0.01	1.563± 0.01	1.489± 0.01	1.538± 0.01
0.903	1.83± 0.01	1.809± 0.01	1.822± 0.01	1.75± 0.01	1.702± 0.01
1	1.967± 0.01	1.936± 0.01	1.958± 0.01	1.895± 0.01	1.867± 0.01
1.079	1.997± 0.01	1.999± 0.01	1.997± 0.01	1.975± 0.01	1.988± 0.01

Mean ± SD, n = 3

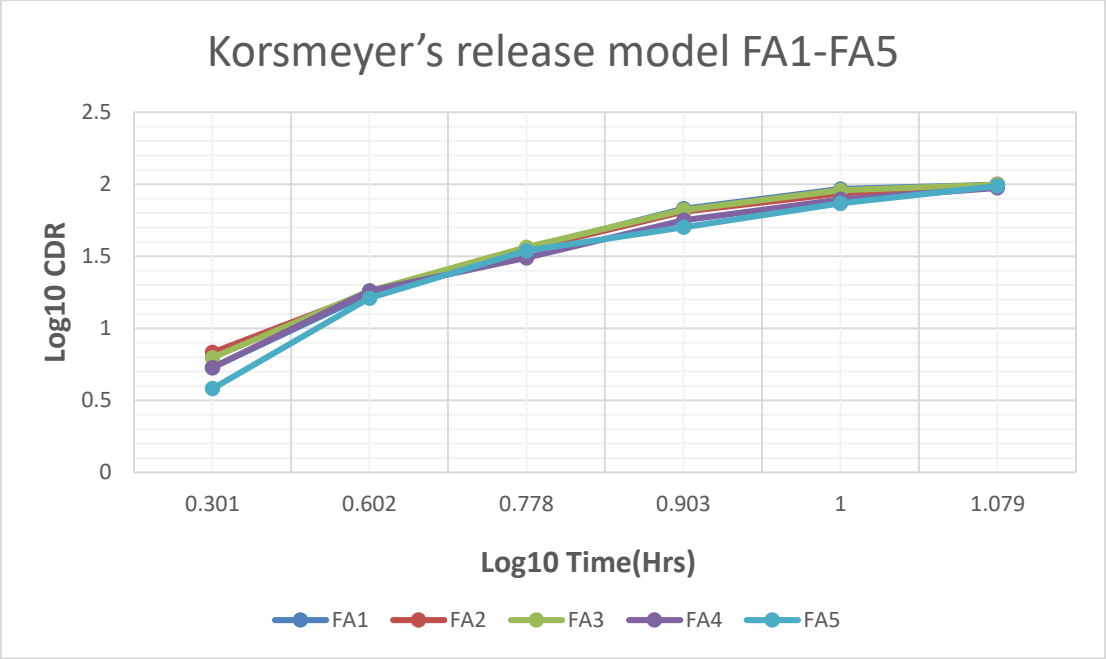

Fig.12:Korsmeyer's release model For Formulations FA1-FA5

Table.12:Korsmeyer's release model (log Cumulative % drug release vs. log time) For Formulations FA6-FA10

Log time	*FA6*	*FA7*	*FA8*	*FA9*	*FA10*
0.301	0.78± 0.01	0.794± 0.01	0.894± 0.01	0.823± 0.01	0.798± 0.01
0.602	1.244± 0.01	1.228± 0.01	1.313± 0.01	1.25± 0.01	1.307± 0.01
0.778	1.514± 0.01	1.559± 0.01	1.536± 0.01	1.45± 0.01	1.661± 0.01
0.903	1.808± 0.01	1.803± 0.01	1.831± 0.01	1.743± 0.01	1.809± 0.01
1	1.921± 0.01	1.913± 0.01	1.919± 0.01	1.881± 0.01	1.928± 0.01
1.079	1.992± 0.01	1.994± 0.01	1.996± 0.01	1.99± 0.01	1.992± 0.01

Mean ± SD, n = 3

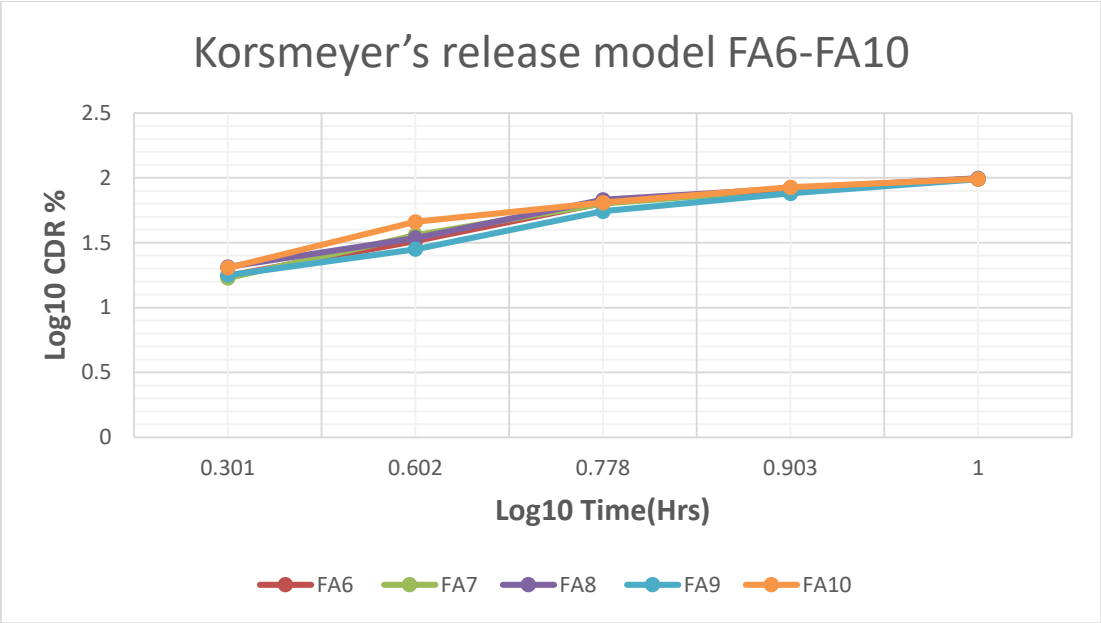

Fig.13: Korsmeyer's release model For Formulations FA6-FA10

Table.13 Regression Values for In-Vitro drug release

S.no	*Zero order plot*	*First Order plot*	*Higuchi's plot*	*Korsmeyer plot*	
	R2	R2	R2	N	R2
FA1	0.9591	0.7611	0.7960	0.0847	0.9915
FA2	0.9687	0.6515	0.8036	0.1313	0.9936
FA3	0.9655	0.7529	0.8050	0.1174	0.9931
FA4	0.9680	0.8089	0.7961	0.0966	0.9963
FA5	0.9651	0.7034	0.7845	0.0333	0.9938
FA6	0.9655	0.7572	0.7980	0.1096	0.9937
FA7	0.97261	0.7362	0.8081	0.1156	0.9943
FA8	0.97108	0.7252	0.8163	0.1690	0.9915
FA9	0.9588	0.7095	0.7795	0.1299	0.9923
FA10	0.9838	0.7866	0.8421	0.1373	0.9881

Result and Discussion-

Formulation of TDDS using polymers, plasticizers and enhancers were done by solvent casting method. It was observed that PVA:PVP in combination with plasticizer Polyethylene glycol-400 dissolved in solvent system Methanol:Water in 30:20 ratio with enhancer Tween 80 at constant temperature of 60°C shown in (Table 1).Another ratio of Plastisizer DMSO and enhancer Span 80 was combined with PVA and PVP in solvent methanol and water (Table 2). The enhancers were selected on the basis of HLB values. The plasticizers in a ratio of 10% w/w PEG400 and 10% w/w DMSO respectively for PVA and PVP were for good flexibility, clarity & elasticity. Characterization of Patches were done for Physiochemical Parameters as shown in (Table 3). The thickness for various formulations for PVA: PVP for the formulations FA1 to FA10 ranged between 0.19±0.01 to 0.29**±0.03**.The weight variation for various formulations ranged between 30.33±1.156 to 32.66±1.165**.**The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The tensile strength of the patches was found to 3.66±1.18 to 5.13±0.13.It is concluded by the results that the tensile strength vary with the nature of polymer and plasticizer. Percentage Elongation ranged between 83.72 to 238. Percentage Swellability ranges 16.97± 0.43 **to**

35.48 ± 0.45 for PVA: PVP Patches when they are kept in distilled water. The surface pH ranges between 5.5 ± 0.14 to **6.0** ± 0.14 pH for all the formulations which is skin pH and hence no skin irritation was expected. Drug content is obtained in specified area of 2 cm^2 using saline phosphate buffer is obtained between 94.99±0.17% to 99.99±0.8%. Almost all medicated transdermal films showed moisture uptake between 3.13±0.36 to 5.57±0.28. Moisture content of FA1 and FA10 films were found in the range of 0.13±0.13 to 1.05±0.13%. Moisture Vapour Transmission is 4.17×10^{-3} to 13.77×10^{-3} for PVA: PVP.

Permeation flux and permeability coefficient of formulated Transdermal patches shown in (Table.4). Hydrophilic polymer (PVA: PVP) FA1 to FA 10 gave flux 0.0788 µg/cm2/hr to 0.2294 µg/cm2/hr respectively. To examine the drug permeation kinetics and mechanism, the data were fitted to models representing zero-order; first-order, Higuchi and Koresmeyer-Peppas. Permeation of the drug from a transdermal drug delivery system mainly involves the factor of diffusion. In our experiments the in vitro permeation profiles of all formulations did not fit into first-order (R^2 = to 0.6515 to 0.8089) they could be best expressed by the Korsmeyer plot for formulation FA1 to FA5 (0.9915 to 0.9963) and between (0.9937-0.9881) for formulations FA6 to FA10.Similarly For Zero order release (R^2 =0.9591 to 0.9838) Higuchi equation (R^2 = 0.7960 to 0.8421) for the permeation of drug from a homogenous-polymer matrix type delivery system that depends mostly on diffusion characteristics. The percent of drug permeated in 12 h was found to be maximum 99.8± 0.01 and 98.98± 0.01 % from formulations FA2 and FA8 respectively.

Conclusion-

In this project Tizanidine Hydrochoride-Diclofenac Sodium transdermal patch were prepared using Polyvinylalcohol, Polyvinylpyyrolidone, plastisizer Polyethylene glycol-400 and Dimethylsulfoxide with penetration enhancers Span 80 and Tween 80 in solvent system methanol: water. Evaluation undergoing various identification and conformation parameters proved that all the preparations FA1 to FA10 shows good *in-vitro* properties. *In vivo* studies using pharmacokinetic and pharmacodynamic parameters confirm that the Formulation FA2 and FA8 are best among all Formulations. Hence the transdermal patch would prove to be a landmark in TDDS for Spasms.

Future Scope-

It is recommended that transdermal drug delivery system may encourage over conventional oral route for obivious advantages and all the formulations are conducible for large scale commercial preparations.

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