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Development and Evaluation of Tizanidine Containing Transdermal Patches for Muscular Pain Management

Jayshree Bairagi[1]*, Sachin K Jain[2], Sudha Vengurlekar[2]

[1]Research Scholar, Oriental University, Near Aurobindo Hospital, Sanwer Road, Indore, MP, India. 453555
[2]Faculty of Pharmacy, Oriental University, Sanwer Road, Indore, MP, India. 453555
*Corresponding author: jayshreebairagi23@gmail.com

Abstract The formulation develops a controlled release polymeric transdermal patch of tizatidine hydrochloride for improving the therapeutic effect of drugs via approaches as transdermal patch hold on to part of skin. All the evaluation data of patch TTP was concluded that polymers have hydrophilic nature and able to enhanced spreadability and dispersibility of the water soluble drug combination for all the monolithic films. The hydrophilic polymer layer produces a water-permeable with more hydrated film. Such hydration allows losing the polymer matrix and consequently enhanced drug release. The effect of penetration enhancers also examined with physical observations and other characterization parameters specifically in-vitro drug release data TTP2, TTP5 and TTP3 were suggested very good result and can reproduce after each interval. The in-vitro value of release exponent "n" was < 1.0 indicating Super-case II transport mechanism. The formulations behavior based on penetration enhancers i.e. mineral oil and plasticizer as PVP with combination of sodium alginate as good supporting polymer for best perfusion release of drug at desired time intervals.

Keywords Tizatidine hydrochloride, Spreadability, Dispersibility, Transdermal patch

Introduction

The oral route is valuable drug delivery system for treatment of diseases conventionally [1]. The literature is compiled upto late 20th century, skin was not known to be a route of drug delivery for systemic drugs. Now days, since last few decades, transdermal drug delivery has potential attention of delivery system due to more advantages over regular use of conventional oral dosage forms. The global market of transdermal drug delivery is estimated to grow and reach approximately $95.57 billion by 2025. This delivery system may improve patient observance because of easy and convenient to apply with a lesser dosing frequency, as the drug is released at a predetermined rate over a prolonged period [2-4]. In the year of 1980s; US Food and Drug Administration (FDA) approved first transdermal system containing scopolamine and nicotine patches in the year of 1984 [5-7]. The researchers and FDA approved a number of transdermal patches for pain relief, analgesic activity, contraception, and hormone replacement therapy [8-9] and the progress in this field continues today.

Advantages

- First pass metabolism of drugs was altered at the site of action through treatment and it can deliver combination of drugs for a lengthened time period [10-13].

- It can achieve better patient compliance and can lessen the side effects in case of inter and intra-patient [11].

Gastric and intestinal fluids degradation of drug may alter blood levels and thus difficult to control for longer period of time. The intravenous infusion release parameters of drug is proportional to TDDS [10-12]

Disadvantages

- Application at site of action may be complicated.
- The drug having water solubility have low penetration rate.

Material and Methods

Pre-formulation studies

The objective of pre-formulation study is to develop the elegant, stable, safe and effective dosage form by establishing compatibility with the other ingredients and to establish physicochemical parameters of new drug substance. The preformulation studies were carried out in terms of tests for identification (physical appearance, melting point, IR spectra and UV spectrum), solubility profile, drug excipients interaction. The drug sample of tizanidine hydrochloride was obtained as a gift sample from Alembic Pharmaceuticals, Ahmedabad India.

Organoleptic parameters identification

Organoleptic parameters of tizanidine hydrochloride were checked by visual inspection

Table 1: Organoleptic Parameters

S. No.	Parameters	Observation
1.	Colour	Off white to light yellowish
2.	Odour	Faint odor
3.	Taste	Bitter

Melting Point determination

The melting range of tizanidine hydrochloride was determined using open capillary method. The drug powder was packed into capillary and melting range was determined by digital melting point apparatus.

Table 2: Melting point of tizanidine hydrochloride

Drug	Melting Point	
	Standard	Experimental
Tizanidine Hydrochloride	280°C	278-280°C

Solubility studies of tizanidine hydrochloride

The solubility of tizanidine hydrochloride was tested in various common solvents. A small quantity of drug was dissolved in 5 ml, until the drug was saturated in solvents and kept for 24 h at room temperature. The solution was filtered and solubility was observed by the UV spectroscopy.

Table 3: Solubility studies in various solvents of drug

S. No.	Solvents	Solubility
1.	Water	0.125
2.	0.1 N HCl	0.105
3.	Phosphate buffer pH 4.5	0.0113
4.	Phosphate buffer pH 6.8	0.0056
5.	Phosphate buffer pH 7.4	0.3294

Partition Coefficient

The partition coefficient of tizanidine hydrochloride was examined in n-octanol: Phosphate buffer pH 7.4 system. It was determined by taking 10mg of drug in separating funnel, containing 10ml of n- octanol and 10ml of Phosphate

buffer pH 7.4. The separating funnel was shaken for 1 hour. Two phases were separated and the amount of drug in aqueous phase was analyzed spectrometrically at 320 nm after appropriated dilution.

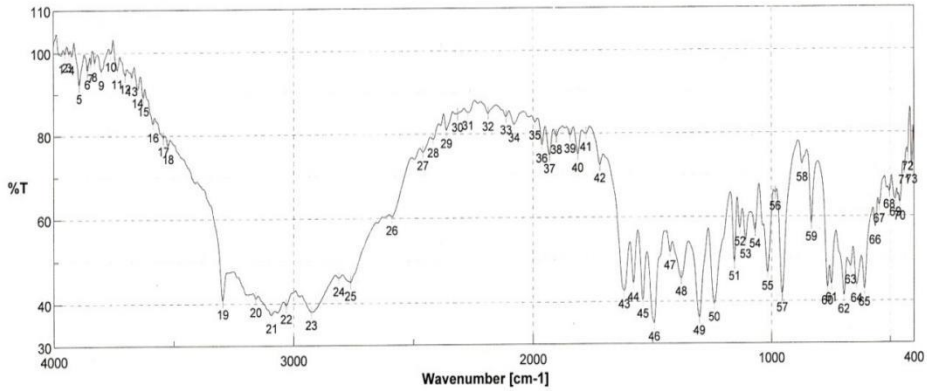
$$\textbf{Partition coefficient} = \frac{\textbf{concentration of drug in organic phase}}{\textbf{concentration of drug in Phosphate buffer pH 7.4}}$$

Table 4: Partition Coefficient of drug

S. No.	Medium	Partition Coefficient	
		Observed	**Reported**
1.	n-octanol : Phosphate buffer pH 7.4	2.04±0.216	2.1

Infra-Red Spectroscopy (IR)

IR spectrum of tizanidine hydrochloride was determined in a FTIR spectroscope (Perkin Elmer-Spectrum RX-I FTIR Spectrophotometer, USA) using KBr pellet. The KBr discs were scanned to obtained FTIR of drug at a resolution of 4 cm^{-1}, from 4000 to 600 cm^{-1}



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3967.82	99.4422	2	3952.39	99.7642	3	3936.97	99.8033	4	3925.39	99.2355	5	3894.54	92.2244
6	3859.83	95.6923	7	3846.33	97.208	8	3829.94	97.5175	9	3801.97	95.4911	10	3762.44	99.9065
11	3736.4	95.6696	12	3702.66	94.4686	13	3674.69	93.9618	14	3650.59	91.0994	15	3626.48	89.1166
16	3585.98	82.7795	17	3542.59	79.4588	18	3523.31	77.6108	19	3294.79	40.8135	20	3156.9	41.2772
21	3091.33	37.3478	22	3030.59	39.5593	23	2925.48	38.0491	24	2810.74	46.0147	25	2761.56	44.9555
26	2588.97	60.34	27	2459.76	75.6917	28	2416.37	78.6969	29	2360.44	80.9224	30	2314.16	84.7794
31	2269.81	85.207	32	2185.92	84.9798	33	2111.67	84.102	34	2077.92	82.2569	35	1992.11	82.7972
36	1963.18	77.2793	37	1932.32	74.799	38	1903.4	79.3505	39	1846.51	79.5382	40	1814.69	74.9858
41	1779.97	79.9308	42	1722.12	72.5153	43	1619.91	42.6677	44	1581.34	44.3134	45	1541.81	40.4064
46	1494.56	34.9265	47	1428.03	51.758	48	1380.78	45.6168	49	1305.57	36.3142	50	1242.9	39.5382
51	1157.08	49.1504	52	1133.94	57.314	53	1109.83	54.353	54	1069.33	56.8065	55	1016.3	46.8039
56	983.518	65.6245	57	954.591	41.6915	58	870.703	72.4935	59	832.133	58.3759	60	764.637	43.2525

Figure 1: IR Spectrum of tizanidine hydrochloride drug sample

Table 5: Interpretation of the IR Spectra of tizanidine hydrochloride

S. No	IR signal range (cm^{-1})	Positions of characteristic absorption (cm^{-1})
1	880-550	832
2	1300-1650	1428
3	3300-3400	3350
4	250-1020	1190
5	3000-3100	3030

Drug- excipients compatibility study

This study was performed to determine any physical change in the drug when kept in contact with various formulation excipients. The drug was mixed with the excipients in 1:1 ratio. The drug- excipients mixture was kept in glass vials properly capped and sealed with aluminium caps. Two vials of each sample were kept at room temperature, in the oven at 40°C/75% RH and in refrigerator for one month period. After every week for one month, the vials were withdrawn and any change in physical appearance as well as color of the contents was observed.

Table 6: Drug excipients physical compatibility study

S. No	Blend	Initial Description	Refrigerator (2-8°C)				Room temperature (25°C)				40°C±75%RH			
			1	2	3	4	1	2	3	4	1	2	3	4
1.	Tizanidine hydrochloride	White Powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
2.	Drug+ Excipients	White Powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

Analytical Study:

Determination of Maximum wavelength (λ_{max})

Tizanidine hydrochloride was accurately weighed (50 mg) and transferred to a 50 ml volumetric flask. To this, 50 ml Phosphate buffer pH 7.4 was added to dissolve the drug and the volume was made up to 100ml with Phosphate buffer pH 7.4 to prepare a 1000 µg/ml solution. Then 1ml of this stock solution was pipette into a 10ml volumetric flask and volume made up to the mark with Phosphate buffer pH 7.4 to prepare a 100 µg/ml solution. It was scanned on a double- beam UV- visible spectrophotometer (Shimadzu 1800) between wavelength 200-400 nm and UV spectrum was recorded. Wavelength maxima for the drug were found to be 320 nm.

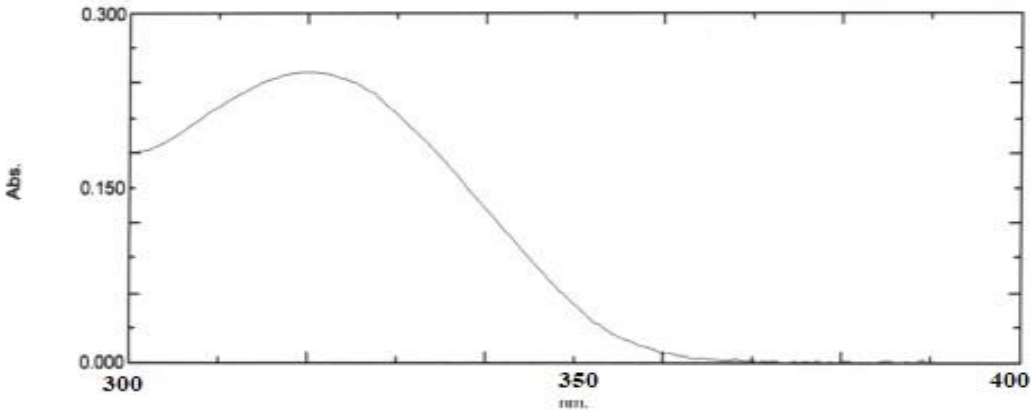


Figure 2: UV spectrum of tizanidine hydrochloride

Calibration Curve of tizanidine hydrochloride in Phosphate buffer pH 7.4

Tizanidine hydrochloride was accurately weighed (100mg) and transferred to 100ml volumetric flask. To this 50ml of Phosphate buffer pH 7.4 was added to dissolve the drug and the volume was made up to 100ml with Phosphate buffer pH 7.4 to prepare 1000µg/ml solution. Then 1ml of this stock solution was pipette into a 10ml volumetric flask and volume made up to the mark with Phosphate buffer pH 7.4 to prepare a 100 µg/ml solution. Appropriate dilutions from the stock solution were made in concentration range of 20-100 µg/ml. The absorbance was noted taken against reagent blank.

Table 7: Calibration curve of tizanidine hydrochloride in Phosphate buffer pH 7.4

S. No.	Concentration (mcg/ml)	Absorbance (mean) ± SD=3
1	0	0
2	5	0.169± 0.002
3	10	0.34± 0.007
4	15	0.467± 0.005
5	20	0.634± 0.004
6	25	0.762± 0.006

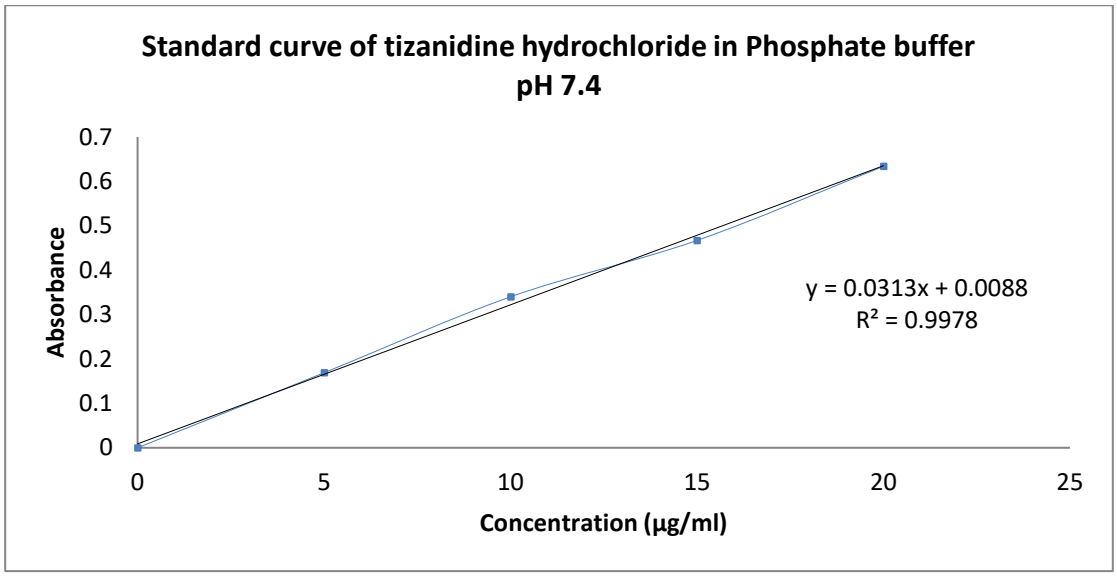


Figure 3: Calibration curve of tizanidine hydrochloride in phosphate buffer pH 7.4

Development and Evaluation of Transdermal Patches

Preparation of the TDDS

The polymeric TDDS were prepared by using hydophillic polymers by solvent casting method, the polymers i.e. sodium alginate and methyl cellulose were dissolved in ethanol: distilled water (1:2) ratio as casting solvent. Chitosan was dissolved in acetic acid aqueous solution (1%) act as the casting solvent. The effect of penetration enhancers was identified by using Isopropyl myristate, Propylene glycol and Mineral oil were selected as penetration enhancers for the preparation of transdermal patch. The API contain tizanidine hydrochloride (4 mg) were dissolved in 1/3rd part of ethanol: distilled water mixture in a closed system with continuous stirring using a magnetic stirrer (Magnetic stirrers, Sistronic Corporation, India). The plasticizers PVP were added with stirring. The contents were kept on continued stirring to ensure complete mixing of the materials. After stirring, it was sonicated in ultrasonic water bath and poured in petri dishes having circular glass bangles open at both end. The bottom of the bangle was wrapped with aluminum foil to hold the casting mixture and other circumference kept open to allow for solvent evaporation at 35°C (Olven Instruments, India). The dried patches were separated, cut into 2 cm^2 diameter (6 mg drug combination), wrapped in aluminum foil and stored in air tight polyethylene bags in desiccators.

Table 8: Preparation of transdermal patch (TNP1 – TNP9)

Formulation Code	Amount (g)				Amount (ml)			Amount (g)
	Drug	Polymers			Penetration enhancers			Plasticizer
	(RT)	Sodium alginate	Ethyl cellulose	Guargum	Isopropyl myristate	Clove oil	Etylene glycol	Glycerol
TNP1	1	3	-	-	0.5			1
TNP2	1	3	-	-		0.5		1
TNP3	1	3	-	-			0.5	1
TNP4	1	-	3	-	0.5			1
TNP5	1	-	3	-		0.5		1
TNP6	1	-	3	-			0.5	1
TNP7	1	-	-	3	0.5			1
TNP8	1	-	-	3		0.5		1
TNP9	1	-	-	3			0.5	1

Physical properties transdermal patch (TNP)**:**

Physical appearance: The physical parameters flexibility, smoothness and transparency were observed.

Thickness: Thickness of transdermal patch was measured by using a screw gauge having least count of 0.02 mm.

Weight variation: The weight of identified transdermal patch was weighed very carefully. The average weight of transdermal patch was calculated.

Surface pH: The surface pH of the transdermal patch was determined by placing the probe of the pH meter in close contact with the wetted surface of the patch.

Tensile strength and percentage elongation: Tensile strength and percent elongation of the transdermal patch were determined on tensile strength testing apparatus. Tensile strength of 2 cm^2 diameter film was measured by using fabricated tensile strength apparatus. The films were fixed between bonding agent tapes and placed in the film holder. A small hole was made in the adhesive tape in which a hook was inserted. A thread was tied to this hook. This hook was passed over the pulley and a small pin attached to the other end to the hold the weights. A small pointer was attached to the thread, which travels over the graph paper affixed on the base plate. The evaluated polymeric films were trailed by dragging system. Now add the weights from initial low mass to the more until the film was broken. The weight required to break the film was noted as break force and tensile strength calculated by the following formulae.

Tensile strength (N / mm^2) = Breaking force (N) / Cross sectional area of sample (mm^2)

The Percentage elongation: Length before the break point / Original length of each step * 100

Folding endurance

The folding acceptance power of prepared transdermal patch was measured manually. A piece of transdermal patch was cut with the help of knife. Strip repeatedly folded at the same place till it broke. The number of times the transdermal patch was folded at the same place without breaking gave the value of the folding endurance.

Swelling Ratio

The effect of polymers combination was identified by swellability effect of the transdermal patch. The prepared transdermal patch was kept in double distilled water in a petri dish. The swelling nature of transdermal patch was observed when in contact with water for specified time. The increase in weight of the eachtransdermal patch at specific time intervals was determined. The transdermal patchwere kept in water upto constant weight of film was observed. The degree of swelling (SR %) was calculated using the following formula

$$\textbf{SR (\%)} = \frac{\text{The weight of the swollen patch at different time intervals}}{\text{The weight of dry transdermal patch}} \times 100$$

Moisture uptake percentage

A piece of transdermal patch was cut with the help of knife. The piece so cut of film was weighed at initial level. After weighing the mass of film, it was kept in desiccators having Saturated Potassium Chloride Solution at 25-30°C, 75% RH for 24h. The transdermal patch were sweeping out from desiccators and reweighed the upgraded mass. The Moisture uptake property of prepared transdermal patch was calculated using the following formulae.

$$\textbf{Moisture uptake (\%)} = \frac{\text{Final weight of Patch - Initial weight of Patch}}{\text{Initial weight of Patch}} \times 100$$

Drug content

A specified area of transdermal patch (2 cm^2 diameter) was kept in 100 ml of dissolution medium and shaken continuously for 24 h. Then the whole solution was ultra sonicated for 15 min, filtered the residue and prepared suitable dilution with same dissolution medium. The solutions were observed by UV spectrophotometric method for estimation of tizatidine hydrochloride.

Result & Discussion

Table 9: Physical characterization of transdermal patch (TNP)

Formulation code	Flexibility	Smoothness	Transparency
TNP1	Soft	Smooth	Translucent
TNP2	Flexible	Smooth	Opaque
TNP3	Flexible	Smooth	Opaque
TNP4	Hard	Rough	Transparent
TNP5	Flexible	Smooth	Transparent
TNP6	Hard	Rough	Opaque
TNP7	Soft	Smooth	Transparent
TNP8	Soft	Smooth	Translucent
TNP9	Hard	Rough	Opaque

Table 10: Thickness of transdermal patch (TNP)

Formulation code	Thickness (mm)
TNP1	0.41±0.01
TNP2	0.44±0.02
TNP3	0.42±0.01
TNP4	0.46±0.02
TNP5	0.44±0.02
TNP6	0.42±0.01
TNP7	0.41±0.02
TNP8	0.46±0.03
TNP9	0.41±0.02
Mean ± SD, n = 3	

Table 11: Weight variation of transdermal patch (TNP)

Formulation code	Average weight (mg)
TNP1	111.32±1.121
TNP2	114.21±1.131
TNP3	116.37±1.134
TNP4	117.22±1.116
TNP5	118.33±1.135
TNP6	114.41±0.111
TNP7	116.20±0.124
TNP8	114.22±1.115
TNP9	113.23±1.112
Mean ± SD, n = 3	

Table 12: Surface pH of transdermal patch (TNP)

Formulation code	Surface pH
TNP1	5.4 ± 0.13
TNP2	5.7± 0.11
TNP3	5.5 ± 0.13
TNP4	5.5 ± 0.13
TNP5	5.4 ± 0.12
TNP6	5.6 ± 0.13

TNP7	5.6 ± 0.11
TNP8	5.4 ± 0.13
TNP9	5.5 ± 0.11
Mean ± SD, n = 3	

Table 13: Percentage Elongation of transdermal patch (TNP)

Formulation code	Percentage Elongation
TNP1	93.74±0.02
TNP2	108.12± 0.02
TNP3	112.62±0.14
TNP4	114.13± 0.02
TNP5	118.12± 0.03
TNP6	99.12±0.15
TNP7	103.01± 0.100
TNP8	105.13±0.02
TNP9	98.71±0.05
Mean ± SD, n = 3	

Table 14: Tensile Strength of transdermal patch (TNP)

Formulation code	Tensile Strength N/mm^2
TNP1	4.66±1.08
TNP2	5.79±0.23
TNP3	6.76±1.11
TNP4	7.19±0.23
TNP5	7.16±1.12
TNP6	6.19±0.03
TNP7	6.03±0.03
TNP8	6.33±0.11
TNP9	5.63 ±0.11
Mean ± SD, n = 3	

Table 15: Folding endurance of transdermal patch (TNP)

Formulation code	Folding endurance
TNP1	85-90
TNP2	99-100
TNP3	95-101
TNP4	96-108
TNP5	100-103
TNP6	99-100
TNP7	94-99
TNP8	97-104
TNP9	92-99
Mean ± SD, n = 3	

Table 16: Swelling ratio of transdermal patch (TNP)

Formulation code	Swelling ratio (%)
TNP1	18.17± 0.13
TNP2	32.13 ± 0.21
TNP3	30.13 ± 0.15
TNP4	21.82 ± 0.19
TNP5	29.02 ± 0.17
TNP6	28.17 ± 0.26
TNP7	18.08 ± 0.38
TNP8	23.13 ± 0.34
TNP9	22.18 ± 0.15
Mean ± SD, n = 3	

Table 17: Moisture content (%) of transdermal patch (TNP)

Formulation code	Moisture Content (%)
TNP1	2.12± 0.13
TNP2	4.19 ± 0.07
TNP3	4.11 ± 0.05
TNP4	2.44 ± 0.01
TNP5	3.86± 0.11
TNP6	3.02 ± 0.02
TNP7	3.08 ± 0.12
TNP8	3.12± 0.12
TNP9	3.19 ± 0.10
Mean ± SD, n = 3	

Table 18: Moisture uptake (%) of transdermal patch (TNP)

Formulation code	Moisture Uptake (%)
TNP1	2.65± 0.23
TNP2	4.93 ± 0.23
TNP3	3.94 ± 0.25
TNP4	2.70 ± 0.29
TNP5	5.61± 0.111
TNP6	3.81 ± 0.22
TNP7	2.90 ± 0.11
TNP8	4.81 ± 0.54
TNP9	3.88 ± 0.24
Mean ± SD, n = 3	

Table 19: Drug content of transdermal patch (TNP)

Formulation code	Drug content of films (%)
TNP1	95.99±0.8
TNP2	94.85±0.7
TNP3	96.99±0.10
TNP4	98.89±0.11
TNP5	99.57±0.14

TNP6	93.55±0.14
TNP7	98.99±0.17
TNP8	93.12±0.8
TNP9	93.82±0.12
Mean ± SD, n = 3	

Preformulation studies are the first step for the rational development of dosage forms of model drug substances. It is an investigation of physical and chemical properties of drug substances alone and in combination with excipients in research. The overall objective of preformulation studies is to produce information constructive to the formulator in development of stable and bioavailable dosage forms. Tizanidine hydrochloride was found to be white, practically odorless, Vertigo metallic tastein nature. The microscopic examination of the drug sample was crystalline powder. The melting point of drug was 208°C. The partition coefficient of drug was found to be 2.5 and the value of partition coefficient of drug showed that the drug was hydrophillic in nature. The Infrared spectra were obtained using an FTIR spectrometer. Drug and other Excipients were weighed as per ratio and passed through sieve # 40, mixed well. The blend was filled in amber color glass vials and stopped with grey rubber stoppers followed by aluminium seal. The drug was estimated in-vitro by reported UV spectrophotometric methods. The reported UV spectrophotometric methods were slightly modified and optimized according to the existing laboratory conditions. The drugs were estimated in the dissolution medium pH 7.4 phosphate buffer. The calibration curves in the dissolution medium i.e. pH 7.4 phosphate buffer prepared with drug solutions of known concentrations. The absorbance of each solution was measured separately at 320 nm for tizatidine hydrochloride. The absorbance was measured and standard curve was plotted between absorbance vs. concentration. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.99. The curves were found to be recti-linear in the concentration range **20 µg / ml to 100 µg / ml** for the drug. All the prepared TNP1 – TNP9 were flexible, smooth, opaque and non sticky in nature. .The prepared polymeric base films were characterized a number of optimized parameters i.e. "optical checking, smoothness color, transparency and flexibility, Thickness of polymeric patch, Weight Variation of patch, Surface pH of patch, Tensile strength of patch, Percentage elongation, Folding endurance, Swelling Ratio of patch, Moisture Content and Moisture uptake Percentage. The values obtained after the examination identified, that polymers have hydrophilic nature and able to enhanced spreadability and dispersibility of the drug combination for all the monolithic films. The hydrophilic polymer layer produces a water-permeable with more hydrated film. Such hydration allows losing the polymer matrix and consequently enhanced drug release. The effect of penetration enhancers also examined after selecting a best formulations from base medicated films i.e. TNP2, TNP5 and TNP3. All formulation showed very good result and can reproduce after each interval.

Summary and Conclusion

The proposed drug is suitable for sustained action as transdermally active system for the management and inhibits polysynaptic reflexes and reduces muscle tone, muscle spasms without reducing muscle strength. Tizanidine is a well-used Clonidine congener, active against α2-adrenergic receptor. The transdermal route delivery system will able to management dementia in people with muscular pain disease for better administration of drugs via transdermal route. The formulation develops a controlled release polymeric transdermal patch of tizatidine hydrochloride for improving the therapeutic effect of drugs via approaches as transdermal patch hold on to part of skin. All the evaluation data of patch TTP was concluded that polymers have hydrophilic nature and able to enhanced spreadability and dispersibility of the water soluble drug combination for all the monolithic films. The hydrophilic polymer layer produces a water-permeable with more hydrated film. Such hydration allows losing the polymer matrix and consequently enhanced drug release. The effect of penetration enhancers also examined with physical observations and other characterization parameters specifically in-vitro drug release data TTP2, TTP5 and TTP3 were suggested very good result and can reproduce after each interval. The in-vitro value of release exponent "n" was < 1.0 indicating Super-case II transport mechanism. The formulations behavior based on penetration

enhancers i.e. mineral oil and plasticizer as PVP with combination of sodium alginate as ood supporting polymer for best perfusion release of drug at desired time intervals.

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