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Fabrication and Evaluation of Matrix Type Novel Transdermal Patch Loaded with Tramadol Hydrochloride

Tramadol Hidroklorür Yüklü Matris Tipi Yeni Transdermal Yamanın İmalatı ve Değerlendirilmesi

Short title: Development of matrix type transdermal patch
Kısa başlık: Matriks tipi transdermal yamanın geliştirilmesi

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ABSTRACT
Objectives: Transdermal drug delivery as a novel drug delivery system (NDDS) has become a major research interest to the scientists for its controlled drug release and improved patient compliance. This work was carried out to develop an optimized transdermal patch of Tramadol hydrochloride using appropriate amount of suitable polymers. It was also planned to control the drug permeation rate from the device to achieve sustained release pattern.
Materials and Methods: Several number of formulations were prepared altering the amount of excipients. Physicochemical and biopharmaceutical parameters were checked to get the optimized formulation with desired characteristics.
Results: Fourier transform infrared (FT-IR) spectroscopy results displayed no abnormal peaks and hence concluded that drug and polymers were compatible with each other. Minimum standard deviation (SD) values of different physicochemical parameters assured that the method of preparation was skilled to formulate patches with least intra batch variability. Higher percentage of hydroxypropyl methylcellulose (HPMC) resulted in the greater tensile strength, moisture content and water vapor transmission rate of the patches. High folding endurance value (>200) indicated about the flexibility of the prepared patches and their integrity to the skin. The transdermal patches coded as F26 containing only HPMC polymer demonstrated the desired drug permeation rate (65.51%) within 12 hour through *ex-vivo* permeation studies.
Conclusion: The formulation coded as F26 was found to be the most optimized patch as

exhibited its drug permeation rate in a sustained manner following higuchi diffusion kinetics that also confirmed about the capability of the formulation to exhibit matrix type drug delivery.
Key words: Optimized transdermal patch, Tramadol hydrochloride, *ex-vivo* permeation studies, Higuchi diffusion kinetics, Matrix type drug delivery.

ÖZ

Amaç: Bir NDDS olarak transdermal ilaç dağıtımı, kontrollü ilaç salınımı ve geliştirilmiş hasta uyumu için bilim adamlarının büyük bir araştırma ilgisi haline geldi. Bu çalışma, uygun miktarda uygun polimerler kullanılarak optimize edilmiş bir Tramadol hidroklorür transdermal yaması geliştirmek için gerçekleştirilmiştir. Ayrıca, sürekli salım modeli elde etmek için cihazdan ilaç geçirgenlik oranının kontrol edilmesi de planlandı.

Materyaller ve Yöntemler: Yardımcı maddelerin miktarı değiştirilerek birkaç formülasyon hazırlanmıştır. İstenen özelliklere sahip optimize edilmiş formülasyonu elde etmek için fizikokimyasal ve biyofarmasötik parametreler kontrol edildi.

Sonuçlar: FT-IR sonuçları anormal tepe noktaları göstermedi ve dolayısıyla ilaç ve polimerlerin birbiriyle uyumlu olduğu sonucuna vardı. Farklı fizikokimyasal parametrelerin minimum SD değerleri, hazırlama yönteminin en az parti içi değişkenlik ile yamaları formüle etme becerisine sahip olmasını sağlamıştır. HPMC'nin daha yüksek yüzdesi, yamaların daha yüksek gerilme mukavemeti, nem içeriği ve su buharı iletim hızı ile sonuçlanmıştır. Yüksek katlanma dayanıklılık değeri (>200), hazırlanan yamaların esnekliğini ve cilde bütünlüğünü gösterir. Yalnızca HPMC polimeri içeren F26 olarak kodlanan transdermal yamalar, ex-vivo geçirgenlik çalışmaları yoluyla 12 saat içinde istenen ilaç geçirgenlik oranını (%65.51) göstermiştir.

Sonuç: F26 olarak kodlanan formülasyonun, aynı zamanda formülasyonun matris tipi ilaç iletimi sergileme kabiliyetini de doğrulayan higuchi difüzyon kinetiğinin ardından sürekli bir şekilde ilaç geçirgenlik oranını sergilediği için en optimize edilmiş yama olduğu bulundu.

Anahtar kelimeler: Optimize edilmiş transdermal yama, Tramadol hidroklorür, ex-vivo permeasyon çalışmaları, Higuchi difüzyon kinetiği, Matriks tipi ilaç dağıtımı.

INTRODUCTION

In the recent few years, there is a research interest has been evolved to design a wide variety of novel drug delivery systems using the existing drug molecules.[1] Currently transdermal drug delivery is considered as one of the most promising approaches for the implementation of NDDS.[2] Topical dosage forms containing one or more therapeutic agents which can produce a systemic effect of the agent is termed as transdermal drug delivery system.[3] There are several advantages of transdermal drug delivery system (TDDS) like controlled release of the drug, steady blood-level profile, minimized systemic side effects, bypassing first-pass hepatic metabolism, self-administration, enhanced patient compliance, improved efficacy over any other conventional dosage forms.[1] Transdermal system has been designed for delivering an effective amount of drug across the intact skin to accomplish both the local and systemic effects.[4] Pain, hypertension, motion sickness, angina, nicotine addiction are the diseases which can be treated by the aid of transdermal delivery of drugs. Latest example of successfully utilizing this system is healing of urinary incontinency and contraception.[5] Transderm SCOP approved by Food and Drug Administration (FDA) in 1979 was the first transdermal system which was used to inhibit nausea and vomiting associated with motion sickness.[1] Creams, ointments, pastes, gels, lotions, sprays, patches are the most common transdermal formulations available in the market.

Transdermal patch is a user friendly, convenient and extensively accepted medicated adhesive device that distributes the drug through the skin for systemic effects at a controlled and

programmed manner.[6] Exposing of patch application site should be avoided from the external heat sources such as hot water bottles, hot water bags etc. Higher body temperature may also elevate the rate of drug release. In this case, patch must be removed immediately.[1] Restricting nature of skin is one of the significant drawbacks for passive delivery of drugs through transdermal patches.[7] Transdermal patches are classified into three types as the drug (i) in a reservoir system, (ii) in adhesive, (iii) in matrix.

The drug in matrix systems are developed by dispersing or dissolving the active pharmaceutical ingredient in a polymer matrix followed by adding an adhesive layer if desired. The polymer matrix regulates the rate of drug delivery.[8,9] The selection of a polymer depends upon its physicochemical properties, compatibility with drug, optimization of the drug loaded into the matrix with other ingredients, skin contact, mode of drug release, and stability.[10,11] Ideal drug candidates for transdermal patch that can readily permeate to the skin must have a low molecular weight, high therapeutic potency, be moderately lipophilic as well as being non-allergenic, and non-irritating.[7] Tramadol hydrochloride is a 4-phenyl-piperidine analogue of opioid drug codeine, 2-(dimethyl amino)-methyl)-1-(3′-methoxyphenyl) cyclohexanol hydrochloride which was first synthesized in 1962.[12] The drug is categorized as an analgesic and can be used to relieve from moderate to severe acute and chronic (cancer and non-cancer) pain, osteoarthritis. For the treatment of dental pain, osteoarthritis flare pain, chronic back pain tramadol provides rapid onset and prolonged action in combination with paracetamol.[13] It has been evidenced that at small dosages tramadol hydrochloride is an effective and safe treatment protocol for premature ejaculation, a common sexual disorder.[14] The study carried out by Chandak and Verma[15] indicated that the matrix type transdermal patches of tramadol fabricated with different grades and altered ratios of HPMC embraced adequate potential for transdermal delivery owing to controlled release pattern of drug from the patches and on the aegis of their in-vitro and pharmacokinetic results. The recent experimental studies had been shown that the transdermal patch containing HPMC, as polymer in higher concentration caused an increased drug release.[16] The present work focused on the development of an optimized sustained release transdermal patch of Tramadol hydrochloride with suitable physicochemical properties and desired release kinetics.

MATERIALS AND METHODS

Tramadol hydrochloride was purchased from Emmennar Pharma Pvt. Ltd. (Visakhapatnam, India). Potassium dihydrogen orthophosphate, Sodium hydroxide, Triethyl citrate, HPMC E15, Ethyl cellulose (EC), Polyvinyl alcohol, Potassium bromide, Potassium chloride, Polyethylene glycol (PEG) 400, n-Octanol, Calcium chloride (fused) were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). HPMC E5 was provided by Colorcon Asia Pvt. Ltd. (Goa, India). Glycerol, Propylene glycol, Methanol were purchased from Merck Specialities Pvt. Ltd. (Mumbai, India). All these ingredients used were of analytical grade except n-Octanol (High performance liquid chromatography grade) and Potassium bromide (Infrared spectroscopy grade).

Identification of Drug

A number of monographic tests (Table 1) were employed as per IP[17] to identify Tramadol hydrochloride which was used as the drug candidate for designing the formulations.

Table 1. Specification required for identification of drug [17]

Tests	Specification
Solubility: In water In methanol In acetone	 Freely soluble Freely soluble Very slightly soluble
Appearance of solution: A 5.0% (w/v) solution of Tramadol hydrochloride	Clear and colorless
Acidity: 0.2 ml of methyl red solution and 0.2 ml of 0.01 M hydrochloric acid was added to 10 ml of 5.0% (w/v) solution of Tramadol hydrochloride. Specified amount of 0.01 M sodium hydroxide was added to change the colour from red to yellow.	Solution will be red in color. Not more than 0.4 ml
Loss on Drying: 1.0 g Tramadol hydrochloride was dried in a hot air oven at 105℃ for 3 h	Not more than 0.5%
Sulfated ash	Not more than 0.1%
Assay: 0.18 g of Tramadol hydrochloride was dissolved in 25 ml of anhydrous acetic acid and 10 ml of acetic anhydride. It was titrated with 0.1 M perchloric acid. The end point was determined potentiometrically. A blank titration was carried out. (1 ml of 0.1 M perchloric acid is equivalent to 0.02998 g of Tramadol hydrochloride)	-----

Compatibility of Drug with Polymers

Compatibility between the drug and polymers were examined using FT-IR spectrophotometer. The infrared (IR) spectra were recorded under a wave range between 4000 – 400 cm^{-1}.[18,19]

Preparation of Backing Membrane

To prepare the backing membrane, 3 g of polyvinyl alcohol was dissolved into 100 ml of distilled water warmed at a temperature 40°C. After filtering the solution 2 ml of filtrate was transferred to each glass mold. It was then placed in a tray dryer at 60°C for 6 hour to get dried.[20]

Formulation of Matrix Type Transdermal Patches

Total 26 batches (F1 – F26) of matrix type transdermal patches were fabricated using

different ratios of HPMC and ethyl cellulose as rate regulatory polymer (Table 2). PEG 400, glycerol, tri-ethyl citrate were used as plasticizers. Propylene glycol was added as an anti-crystalizing agent. The polymers and other excipients in different ratios (Table 2) were dissolved to methanol. 50 mg of Tramadol hydrochloride was added slowly in the polymeric solutions of individual batch and stirred on magnetic stirrer until a uniform mixture was obtained. The mixture was then poured on the glass mold which was covered with a glass funnel of appropriate size to govern evaporation rate of the solvent. The casting solvent was subsequently permitted to evaporate overnight at 40°C for attaining the dried patches.[21] After drying, the patches were cut out from glass mold. A backing membrane was affixed with suitable adhesive and dried at the room temperature. The patches were then kept between sheets of wax paper and stored in desiccators for their evaluation followed by optimization.[22-23]

Table 2. Composition of matrix type transdermal patches (F1 – F26)

Patches	Quantity / Patch (mg)								
	Tramadol HCl	**HPMC E5**	**HPMC E15**	**EC**	**PEG 400**	**Glycerol**	**Propylene glycol**	**Tri-ethyl citrate**	**Total weight (mg)**
F1	50	-	-	50	10	-	-	10	120
F2	50	-	-	100	10	-	-	10	170
F3	50	-	-	100	10	10	-	-	170
F4	50	-	-	100	20	10	-	-	180
F5	50	-	-	100	30	10	-	-	190
F6	50	-	-	100	20	20	-	-	190
F7	50	-	-	150	20	20	-	-	240
F8	50	-	-	200	20	20	-	-	290
F9	50	100	-	-	20	20	-	-	190
F10	50	150	-	-	20	20	-	-	240
F11	50	200	-	-	20	20	-	-	290
F12	50	100	-	100	20	20	-	-	290
F13	50	150	-	100	20	20	-	-	340
F14	50	200	-	100	20	20	-	-	390
F15	50	200	100	-	20	20	-	-	390
F16	50	200	200	-	20	20	-	-	490
F17	50	200	125	-	20	20	-	-	415
F18	50	200	125	-	20	20	10	-	425
F19	50	200	125	-	20	20	20	-	435
F20	50	200	125	-	20	20	15	-	430
F21	50	200	125	-	-	20	10	-	405
F22	50	200	125	-	-	30	10	-	415
F23	50	200	125	-	-	40	10	-	425
F24	50	200	125	-	-	50	10	-	435
F25	50	200	150	-	-	50	10	-	460
F26	50	250	190	-	-	50	10	-	550

Evaluation of Matrix Type Transdermal Patches

Formulated patches were evaluated for different physicochemical parameters such as thickness, drug content, moisture content, moisture uptake, flatness, tensile strength, water vapor transmission (WVT) rate, folding endurance, etc.[1,6,21]

Thickness

Thickness was measured using a digital screw gauge at five distinct portions of the patches from each batch and the mean value including standard deviation was calculated.[24]

Weight variation

Randomly selected ten patches from each batch were subjected to weight variation test. A specified area of the individual patch was cut in different parts and weighed. Average weight and standard deviation was calculated from the weights measured individually.[25]

Drug content

An accurately weighed (100 mg) section of transdermal patch was dissolved in 100 ml of phosphate buffer (pH 7.4) and the solution was then shaken continuously for 24 hour in a shaker incubator followed by sonication for about 15 min. After subsequent filtration and suitable dilution, the drug content in the solution was assessed by using UV-visible spectrophotometer at the wavelength 275 nm.[25,26]

Moisture content

The patches from the individual batch were weighed individually and stored in a dessicator installed with activated silica at room temperature for 24 hour. The patches were then weighed repeatedly until a constant weight was found. Percentage moisture content was measured by using the following formula.[25,27]

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Moisture uptake

A transdermal patch was weighed and placed in a dessicator containing a saturated solution of potassium chloride at room temperature for 24 hour. After completion of the time period, the patch was weighed repeatedly until a constant weight was found. Percentage moisture uptake was measured by using the following formula.[25]

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Flatness

Flatness test was performed to appraise that the formulated patches retain a smooth surface and will not constrict with time. One longitudinal strip was cut from the center and two from either end of the patches which were individually measured. The variation in length caused by non-uniformity in flatness was checked by determining the percent constriction. Zero percent constriction is considered as equivalent to 100 percent flatness. Percentage constriction was calculated by using the following formula.[25,26]

$$\text{Percentage constriction} = \frac{\text{Initial length of strip} - \text{Final length of strip}}{\text{Initial length of strip}} \times 100$$

Folding endurance

Folding endurance of the patches was estimated by repeatedly folding a small section of the patch (2 × 2 cm) at the same place until it cracked. The number of times through which the patch could be folded at the same place without producing any crack line presented the folding endurance value. Three patches from each batch were considered for performing this test.[28]

Tensile strength

Transdermal patches were cut into 1 cm^2 size and placed between two clamps of tensilometer.

Weight was gradually added so that the increasing pulling force could break the film. The force needed to break the patch was recognized as tensile strength expressed in the unit kg/cm^2.[25]

Water vapor transmission (WVT) rate

The quantity of moisture transmitted through unit area of patch in unit time is expressed as WVT rate. Glass vials of equal diameter and volume were used as transmission cells which were washed thoroughly. After drying the vials in a hot air oven, about 1 g of anhydrous fused calcium chloride was taken in each vial, and the patch was affixed over the edge of the vial using a suitable adhesive tape. Weight of the vial was noted and kept in desiccator comprising saturated solution of potassium chloride for maintaining 84% relative humidity (RH). These cells were removed from the desiccators after 24 hour and re-weighed. The water vapor transmission rate was determined as follows[28]

$$\text{WVT rate} = \frac{\text{Weight of water vapor transmitted} \times \text{Thickness of patch}}{\text{Surface area exposed in square meter}}$$

In-vitro Permeation Studies

Modified Franz Diffusion Cell was employed to carry out *in-vitro* permeation studies. Mixed cellulose ester membrane was used as dialysis (barrier) membrane which was previously soaked in distilled water for 24 hour. The transdermal patches were adhered to the dialysis membrane and the membrane was tied firmly to the donor compartment of the diffusion cell. The receptor compartment of the diffusion cell was filled with 85 ml of phosphate buffer (pH 7.4). The donor compartment was lowered to the receptor compartment in such a way that the dialysis membrane just touched the media of the receptor compartment. This assembly was constructed on a magnetic stirrer with heater. Temperature of the receptor compartment was maintained at 37 ± 2 °C. The content of the diffusion cell was continuously stirred using a teflon coated bead at a constant speed of 600 rpm. Samples were withdrawn at specified intervals of time and same amount of phosphate buffer (pH 7.4) was added to maintain the sink condition. After suitable dilution, the samples were examined for percentage drug content using UV-visible spectrophotometer at the wavelength 275 nm.[21] *In-vitro* permeation study was carried out for 6 hour.[29,30]

Ex-vivo Skin Permeation Studies

In *ex-vivo* skin permeation studies, goat skin was used as dialysis (barrier) membrane which was obtained from a local slaughterhouse. The skin was thoroughly cleaned with running tap water followed by eliminating full thickness and non-dermatome skin using a scalpel.[31] It was then soaked in an isotonic solution for 30 min. *Ex-vitro* permeation study was carried out for 12 hour. Procedure mentioned for *in-vitro* permeation studies was followed for performing this studies.[32]

Drug Release Kinetics Study

Data obtained from *in-vitro* and *ex-vivo* permeation studies were fitted to different mathematical models such as zero order, first order, and Higuchi release kinetics to define the kinetics and pattern of drug release.[33]

RESULTS AND DISCUSSION

Identification of Drug

Several monographic tests were performed (Table 3) to check the identity of Tramadol hydrochloride. Obtained results matched satisfactorily with their corresponding specification[17] required. Hence, monographic tests confirmed the identity of Tramadol hydrochloride.

Table 3. Identification of drug by performing several monographic tests

Tests	Obtained Result
Solubility: In water In methanol In acetone	 Freely soluble Freely soluble Very slightly soluble
Appearance of solution: A 5.0% (w/v) solution of Tramadol hydrochloride	Clear and colorless
Acidity: 0.2 ml of methyl red solution and 0.2 ml of 0.01 M hydrochloric acid is added to 10 ml of 5.0% (w/v) solution of Tramadol hydrochloride. Specified amount of 0.01 M sodium hydroxide is added to change the colour from red to yellow.	Red color solution was formed. Yellow color was appeared after adding 0.3 ml
Loss on Drying: 1.0 g Tramadol hydrochloride is dried in a hot air oven at 105°C for 3 h	0.3%
Sulfated ash	0.087%
Assay: 0.18 g of Tramadol hydrochloride is dissolved in 25 ml of anhydrous acetic acid and 10 ml of acetic anhydride. It is titrated with 0.1 M perchloric acid. The end point is determined potentiometrically. A blank titration is carried out. (1 ml of 0.1 M perchloric acid is equivalent to 0.02998 g of Tramadol hydrochloride)	98.13%

Fourier Transform Infrared Spectroscopy (FT-IR)

The drug and polymeric materials were found physically compatible with each other. The characteristic absorption peak obtained from FT-IR spectra of Tramadol hydrochloride (Figure 1) resembled almost the same with the spectra of standard sample of that. It was evidently manifest that the individual characteristics bands of Tramadol hydrochloride (Figure 1), and the polymers HPMC E5 (Figure 2), HPMC E15 (Figure 3), EC (Figure 4) at the particular wavenumbers were also present in the FT-IR spectra analyzed for the physical mixtures of the drug along with these polymers (Figure 5, Table 4). Interpretation from the FT-IR studies directed that the drug was pure, and it was chemically compatible with the polymers used. HPMC, as hydrophilic polymer and EC, as water insoluble polymer was used in the formulations.

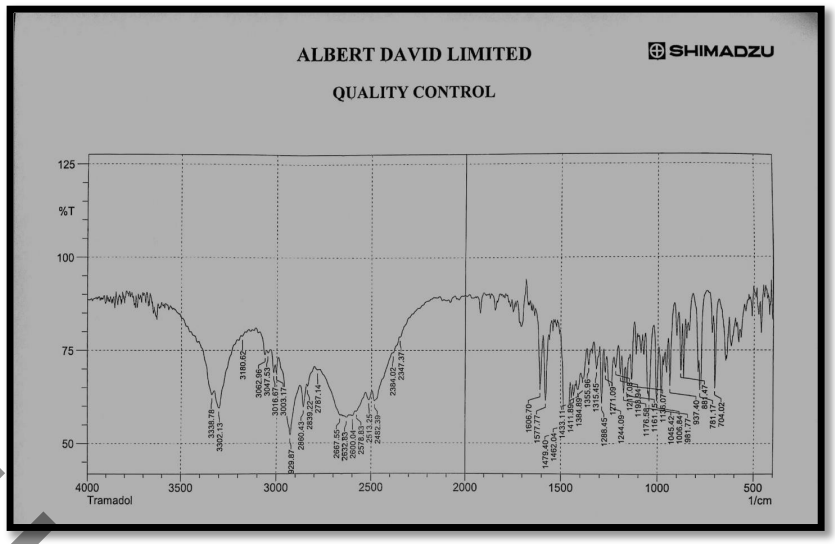


Figure 1. FT-IR spectra of Tramadol hydrochloride

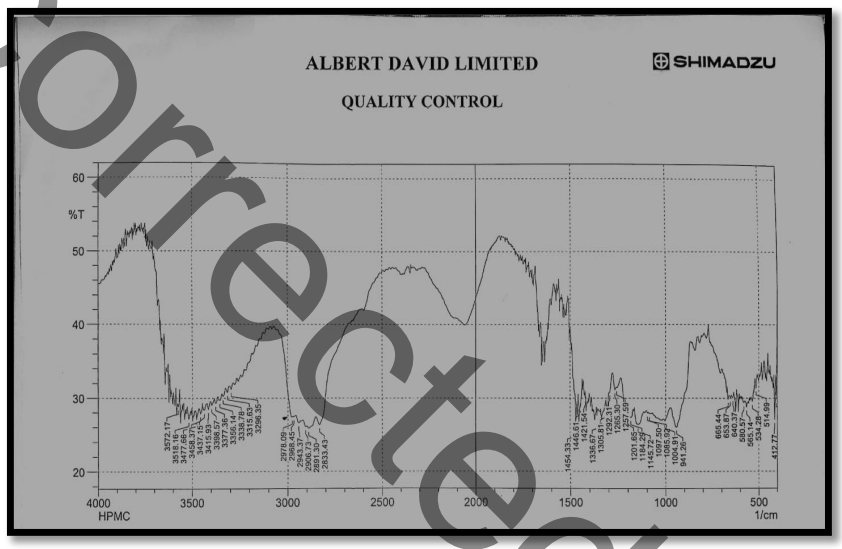


Figure 2. FT-IR spectra of HPMC E5

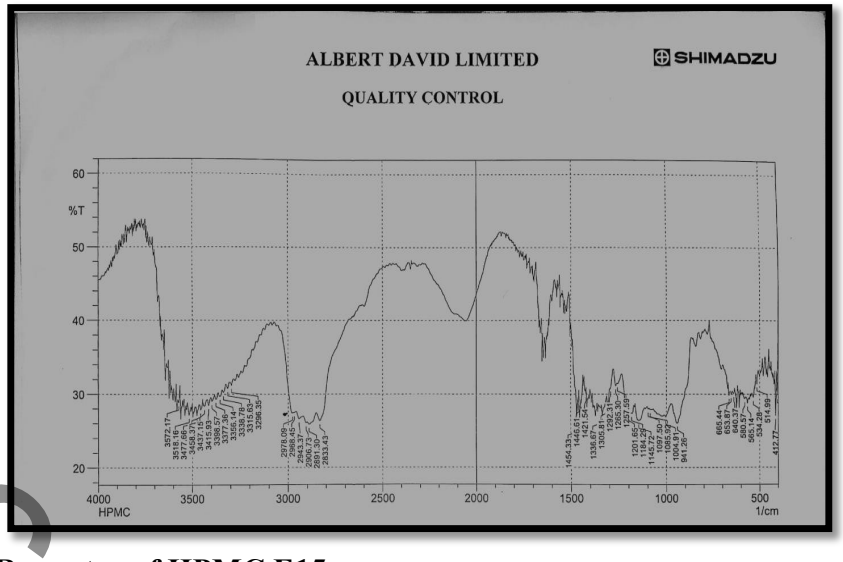


Figure 3. FT-IR spectra of HPMC E15

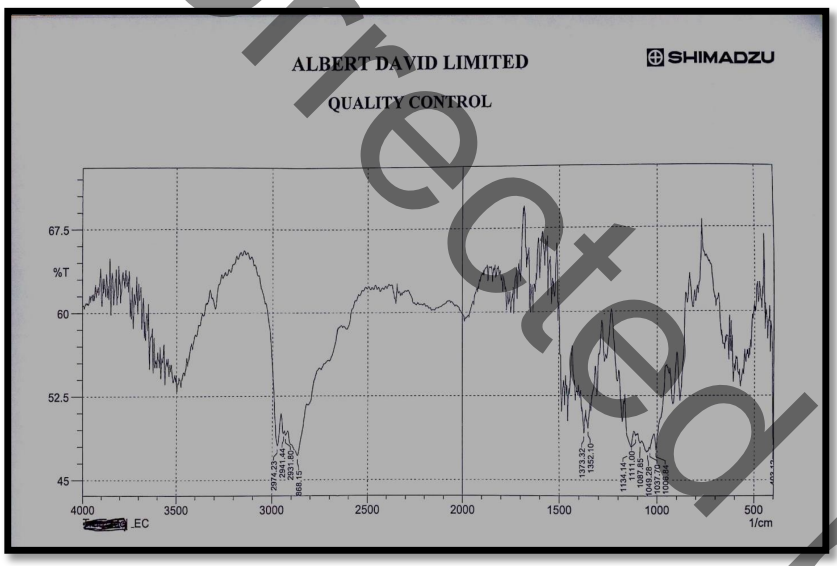


Figure 4. FT-IR spectra of EC

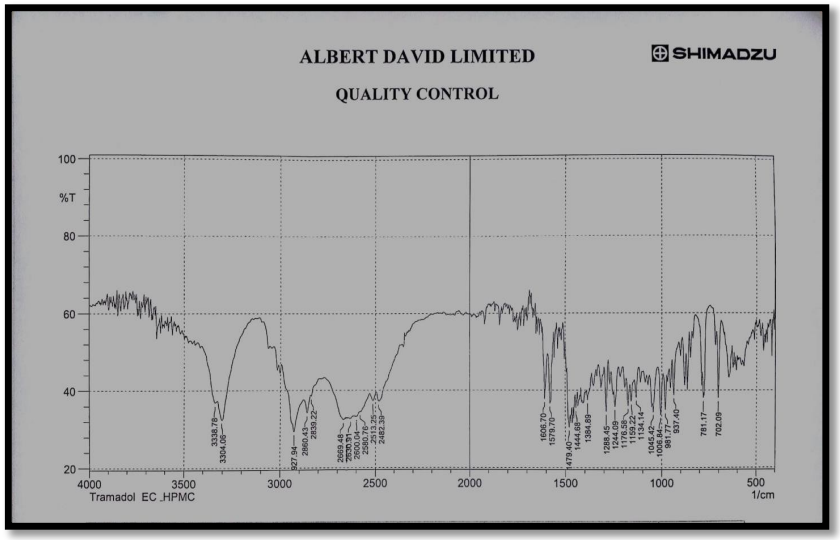


Figure 5. FT-IR spectra of Tramadol hydrochloride along with polymers used

Table 4. Interpretation of FT-IR spectrum

Wave Number of Tramadol hydrochloride (cm^{-1})	Wave Number of HPMC E5 (cm^{-1})	Wave Number of HPMC E15 (cm^{-1})	Wave Number of EC (cm^{-1})	Wave Number of drug along with polymers (cm^{-1})	Interpretation
3047.53	3077.60	3079.41	3080.51	3081.61	C – H Stretching (aromatic)
1577.77	1575.03	1578.36	1579.76	1579.70	C – C Stretching
1479.40	1478.10	1479.08	1479.38	1479.40	- CH_3 Bending
2839.22	2833.43	2833.91	2838.82	2839.22	C – H Stretching
1741.31	1740.22	1741.32	1741.02	1741.52	C = O Stretching
1240.51	1241.02	1240.43	1241.53	1240.58	C – O Stretching

Evaluation of Matrix Type Transdermal Patches

Based on the observations found from the physical appearance for all the batches (F1-F26) of transdermal patches (Table 5), only eleven batches were nominated for evaluation.

Table 5. Physical appearance of the formulated transdermal patches (F1 – F26)

Formulation code	Observation	Remarks
F1	Patch was not formed	Rejected
F2	Patch was formed but became brittle on drying	Rejected
F3	Patch was brittle in nature; crystallization was occurred on drying	Rejected
F4	Patch was not formed	Rejected
F5	Showed crystallization and enhanced brittleness	Rejected
F6	Crystallization was occurred	Rejected
F7	Patch was formed firmly	Selected
F8	Patch was formed firmly	Selected
F9	Patch was not formed	Rejected
F10	Patch was formed, but crystallization was occurred	Rejected

F11	Better than F10, crystallization was occurred in negligible amount	Selected
F12	Better than F10, crystallization was occurred in negligible amount	Selected
F13	Patch was not formed	Rejected
F14	Better than F11 & F12	Selected
F15	Patch was formed firmly	Selected
F16	Patch was formed, but enhanced crystallization was found	Rejected
F17	Patch was formed, but slightly brittle in nature	Rejected
F18	Patch was formed firmly	Selected
F19	Patch was sticky in nature	Rejected
F20	Patch was sticky in nature	Rejected
F21	Patch was more brittle than F17	Rejected
F22	Patch was more brittle than F17	Rejected
F23	Patch was formed firmly	Selected
F24	Patch was formed firmly	Selected
F25	Better patch from all respects	Selected
F26	Better patch from all respects	Selected

Physicochemical Parameters

Thickness of the patches ranged from 0.47 to 0.57 mm (±0.003 to ±0.007) while the average weight of the patches varied from 289.89 to 558.16 mg (±0.40 to ±0.48) (Table 6). These minimum SD values assured that the method of preparation was skilled to formulate patches with least intra batch variability. Satisfactory percentage of drug content with minimum SD value (Table 6) was found throughout all the patches. Table 6 displayed that increased amount of HPMC caused increasing in percentage of moisture content and moisture uptake of the transdermal patches due to hydrophilic properties of HPMC. Patel et al.[23] had been also reported that higher percentage of HPMC resulted in the higher moisture content. However, lower percentage of moisture content of all the batches was capable to prevent the patches from microbial contamination and retard their bulkiness. Flatness of the transdermal patches shown in Table 6 indicated the minimum level constriction just close to zero percent.[1] Folding endurance value was found greater than 200 in all batches with minimum SD value (±0.51 to ±0.58) (Table 7) which proved that the prepared transdermal patches were enough flexible, able to withstand mechanical pressure and proficient to retain the integrity with skin folding after its application. From Table 6 and 7, it was reported that decreasing in the thickness of the patches accomplished higher folding endurance value. The patches containing higher amount of HPMC showed greater tensile strength whereas increasing amount of ethyl cellulose lowered the strength. Limpongsa and Umprayan[34] had been also reported that addition of ethyl cellulose resulted in the lower tensile strength. Due to hydrophilic property of HPMC the films containing higher proportion of HPMC showed greater WVT rate and addition of ethyl cellulose lowered it.

Table 6. Evaluation of physicochemical parameters of selected transdermal patches

Formulation code	Thickness[a] (mm) ± SD	Weight variation[b] (mg) ± SD	Drug content[a] (%) ± SD	Moisture content[b] (%) ± SD	Moisture uptake[b] (%) ± SD

F7	0.49±0.006	289.89±0.41	99.23±0.79	1.19±0.07	2.29±0.07
F8	0.57±0.003	299.42±0.41	99.33±0.61	1.18±0.05	2.28±0.05
F11	0.51±0.004	299.91±0.48	98.93±0.77	1.29±0.07	4.42±0.03
F12	0.51±0.006	300.18±0.40	99.13±0.65	1.22±0.07	4.34±0.03
F14	0.48±0.006	398.77±0.41	98.91±0.78	1.81±0.06	4.94±0.03
F15	0.55±0.005	399.60±0.43	99.09±0.84	2.19±0.04	6.76±0.03
F18	0.50±0.003	434.47±0.47	99.27±0.81	2.56±0.09	6.94±0.03
F23	0.56±0.007	434.50±0.43	99.40±0.72	2.59±0.05	6.97±0.01
F24	0.51±0.006	443.53±0.46	98.96±0.76	2.58±0.06	6.98±0.02
F25	0.53±0.007	468.28±0.47	99.02±0.82	3.08±0.06	7.81±0.08
F26	0.47±0.004	558.16±0.42	99.41±0.60	3.52±0.04	9.94±0.03

All values are expressed as mean S.D, [a]n = 10, [b]n = 5

Table 7. Evaluation of physicochemical parameters of selected transdermal patches

Formulation code	Flatness[a] (%) ± SD	Folding endurance[b] ± SD	Tensile strength[a] (kg/cm^2) ± SD	WVT studies[b] (g/m^2/24 h) ± SD
F7	99.87±0.002	202±0.54	0.51±0.03	1.84±0.02
F8	99.88±0.004	200±0.55	0.46±0.05	1.81±0.01
F11	100.03±0.004	201±0.52	0.63±0.08	1.93±0.05
F12	99.91±0.001	200±0.58	0.52±0.02	1.85±0.07
F14	99.97±0.003	205±0.52	0.57±0.03	1.91±0.04
F15	100.07±0.002	200±0.56	0.68±0.01	2.21±0.08
F18	99.93±0.001	201±0.55	0.70±0.05	2.29±0.07
F23	99.89±0.004	200±0.57	0.69±0.04	2.33±0.08
F24	99.96±0.002	200±0.51	0.69±0.03	2.31±0.05
F25	100.00±0.003	200±0.57	0.73±0.06	2.73±0.04
F26	100.01±0.001	207±0.58	0.87±0.08	3.12±0.08

All values are expressed as mean S.D, [a]n = 10, [b]n = 5

In-vitro and ex-vivo Permeation Studies

Because of their long term release pattern only F14, F18, F23, and F26 batches were selected (Table 8) for *ex-vivo* skin permeation and kinetics study. The results obtained from *in-vitro* permeation studies showed controlled drug release as the concentration of EC decreased. The formulation F26 containing the higher amount of HPMC E5, HPMC E15 as polymers showed rate regulatory drug release pattern as compared to the other formulations. As plasticizer, effect of glycerol was most satisfactory with increased concentration of HPMC in the formulation F26 which showed the controlled *in-vitro* drug release.

Table 8. *In-vitro* permeation study of matrix type transdermal patches

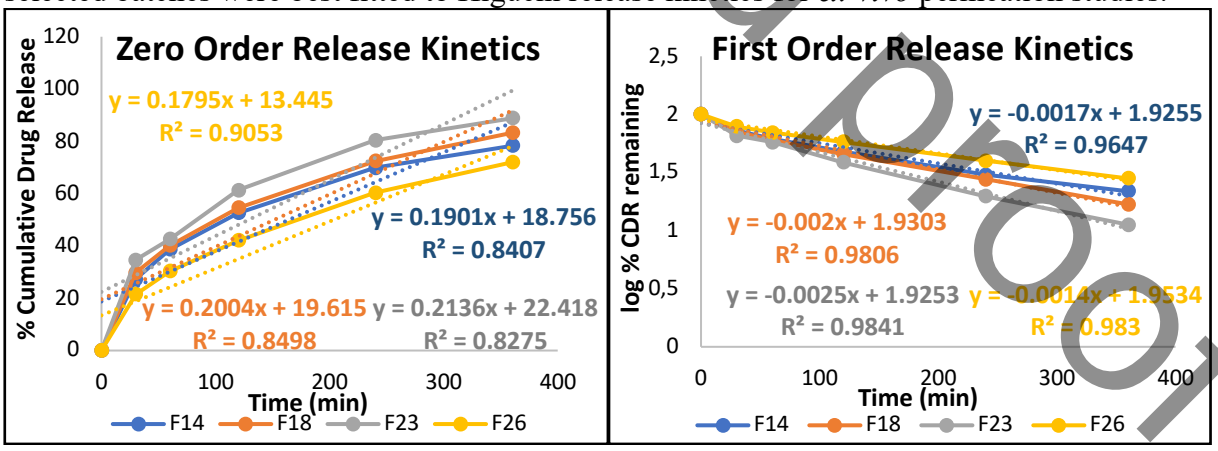
Time (min)	Percentage Cumulative Drug Release										
	F7	F8	F11	F12	F14	F15	F18	F23	F24	F25	F26
0	0	0	0	0	0	0	0	0	0	0	0
30	49.51	26.74	49.76	31.46	27.22	36.62	29.68	34.57	40.21	32.36	21.46
60	85.43	41.87	91.48	68.63	38.64	51.62	40.12	42.55	48.19	45.62	30.26
120	98.52	69.49	90.13	88.67	52.58	68.32	54.54	61.31	66.95	62.74	42.10

240	97.78	86.31	-	87.31	69.83	87.82	72.46	80.35	83.56	85.12	60.28
360	-	93.78	-	-	78.24	101.87	83.22	88.77	94.41	99.63	71.96

Table 9. *Ex-vivo* permeation study of matrix type transdermal patches

Time (min)	Percentage Cumulative Drug Release			
	F14	**F18**	**F23**	**F26**
0	0	0	0	0
30	11.15	15.87	19.67	12.78
60	20.88	24.83	28.56	18.42
120	34.82	35.78	45.71	29.25
240	52.07	52.776	58.51	42.17
360	60.48	63.98	69.87	50.11
480	68.61	72.66	80.78	57.26
720	71.98	75.87	83.71	65.51

Effect of polymers and plasticizers on the results of *ex-vivo* permeation studies was same as the ingredients influenced the results of *in-vitro* permeation studies. Percentage cumulative drug release from the formulations was found more than 60% after 12 hour (Table 9) which was considered satisfactory. *In-vitro* (Table 8) and *ex-vivo* drug release profile (Table 9) of the mentioned batches was fitted into different kinetics model (Figure 6 and 7). The data obtained from Table 10 explained that all the selected batches except F23 were best fitted to Higuchi release kinetics for *in-vitro* permeation studies. The rate of permeation of the drug through goat skin was slower and in sustained manner as compared to *in-vitro* release profile. This could be explained by comparing the thickness of goat skin membrane with that of dialysis membrane used. However, the data obtained from Table 11 clarified that all the selected batches were best fitted to Higuchi release kinetics for *ex-vivo* permeation studies.



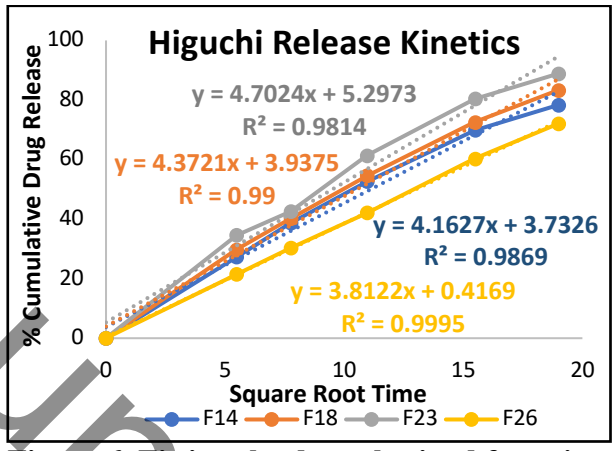


Figure 6. Fitting the data obtained from *in-vitro* permeation study to different kinetics model

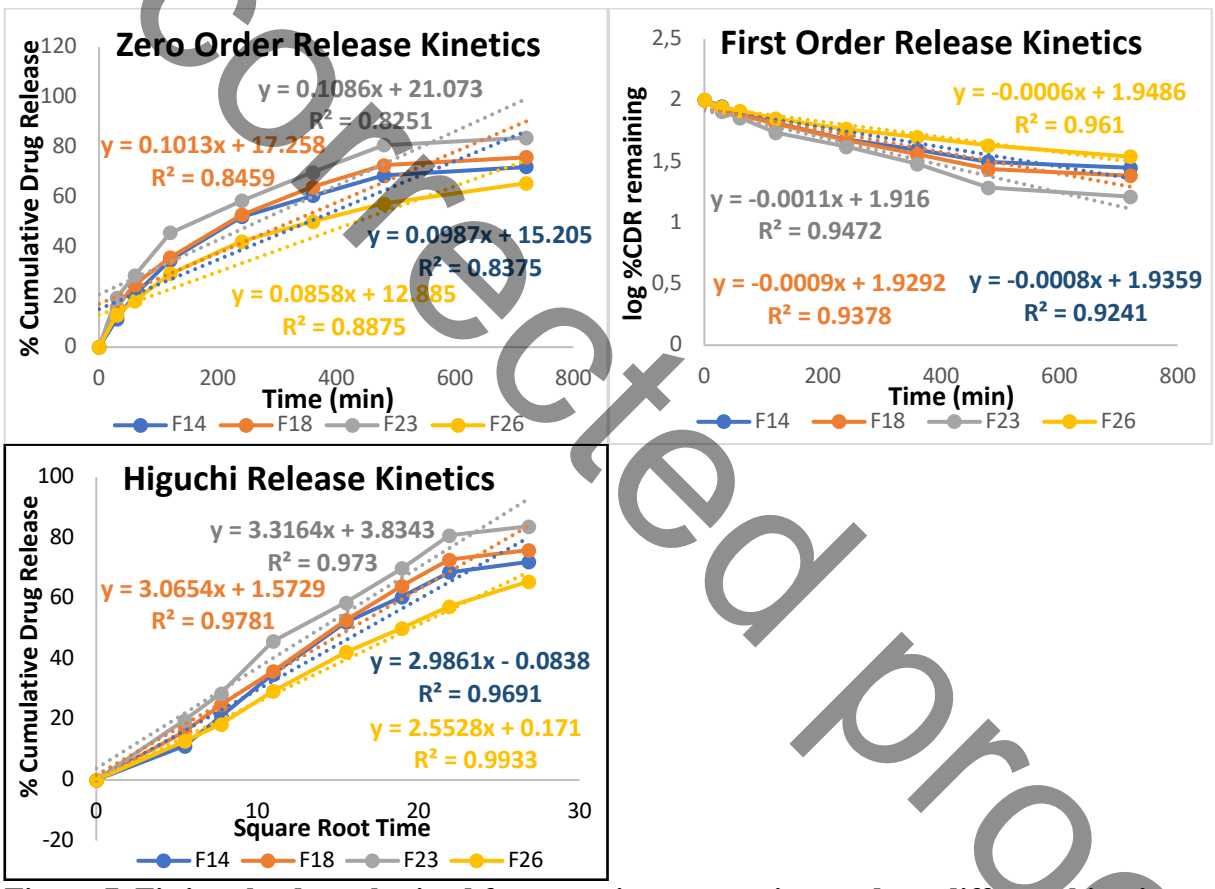


Figure 7. Fitting the data obtained from *ex-vivo* permeation study to different kinetics model

Table 10. Values of correlation coefficient of different kinetics model for *in-vitro* permeation study

Release kinetics	Correlation coefficient (R^2)			
	F14	**F18**	**F23**	**F26**
Zero Order	0.840	0.849	0.827	0.905
First Order	0.964	0.980	0.984	0.983
Higuchi	0.986	0.990	0.981	0.999

Table 11. Values of correlation coefficient of different kinetics model for *ex-vivo* permeation study

Release kinetics	Correlation coefficient (R^2)			
	F14	**F18**	**F23**	**F26**
Zero Order	0.837	0.845	0.825	0.887
First Order	0.924	0.937	0.947	0.961
Higuchi	0.969	0.978	0.973	0.993

Depending upon the results obtained from physicochemical evaluations performed and especially based on the sustained release profile, F26 was designated as the optimized formulation. For this formulation, the best kinetics model was the Higuchi equation, whereas the plots exposed great linearity with highest R^2 values (Figure 6 and 7), suggesting the process of diffusion. Hence it was confirmed that the formulation was capable to exhibit matrix type drug delivery.

CONCLUSION

To achieve better bioavailability and improved patient compliance, optimized matrix type novel transdermal patches containing tramadol hydrochloride were formulated with higher amount of HPMC as rate regulating polymer. As per *ex-vivo* drug release, the concern was that the optimized formulation permeated only 65.51% drug through goat skin within 12 hour (Table 9). This indicated a window for using a permeation enhancer in the formulation to improve the drug permeation rate through goat skin. However, further *ex-vivo* permeation studies are required to find out the suitable permeation enhancer.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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