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Formulation and evaluation of Transdermal patches of Torasemide

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Abstract

The main advantage of Transdermal drug delivery system is to bypass the first pass metabolism, avertance of the risk and annoyance of intravenous therapy and of the varied conditions of absorption, like pH changes, gastric emptying time and presence of enzyme. The Transdermal drug delivery scheme is generally used where the others system of drug administration fails or it is mainly used in edema associates congestive heart failure. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time. This review describes the assorted formulation aspects, a variety of excipients, evaluation tests, challenges and drugs explored in the pasture of topical drug delivery.

Keywords: Transdermal patches, Skin, Controlled Drug Delivery System

1. Introduction

1.1 Controlled drug delivery

Controlled drug delivery technology represents one of the most rapidly advancing areas of science in which chemists and chemical engineers are contributing to human health care. Such delivery systems offers various advantages compared to conventional dosage forms including, improved patient, reduced toxicity, and improved efficacy compliance and convenience.[1]

The different classification of controlled drug delivery systems (CDDS) can be given as follows[2][3]:

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes, first class contains new drug delivery systems as transdermal delivery, ocular inserts, intra uterine delivery and sub dermal implants. The transdermal drug deliveries have advantages to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for long time.

Transdermal patch or adhesive patch or skin patch used to deliver a controlled dose of a drug through the skin over a period of time. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the blood circulation. Few drugs should be combined with substances, like as alcohol that enhances their ability to penetrate the skin in order to be used in the skin patches. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), lidocaine to relieve the pain of shingles and many more drugs.

1.2 Rationale and Objective Study[4][6]:

Some chronic diseases like diabetes, hypertension, tuberculosis, cancer require prolong administration of drugs and frequent dosing to maintain constant drug plasma concentration level and may lead to poor patient compliance. Many orally administered drugs can irritate the GI tract or undergo first pass metabolism and leads to poor bioavailability. This led to development of transdermal drug delivery system (TDDS).

TDDS provides continuous administration of drug through the skin, which maintains constant plasma drug levels and avoids the peaks and troughs seen with oral administration. TDDS offers no first-pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract.

Continuous delivery of drug may reduce systemic side effects associated with high plasma drug levels. The multiday dosing that is made possible by the sustained delivery of drugs with short half-life. It includes a non oral route of administration for patients who are unable to take oral medications and the immediate cessation of drug administration with removal of the patch.

Torasemide is a sulfonyl urea loop diuretic which has been shown to be effective in the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Also used for treatment of hypertension alone. The most frequently reported side effects are gastric disturbances like nausea, anorexia, vomiting, and enhanced appetite after oral treatment. Because these drugs are generally intended to take for a long period, patient compliance is very important. The plasma half life of this drug is very short i.e. about 3.5 hours which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long term treatment. Therefore to avoid conventional multiple oral dosing, controlled release transdermal patch of Torasemide can be prepared.

1.3 Objective of the study[7]

a) Preparation of matrix transdermal patches by using combination of appropriate polymers.
b) To study the effect of varying concentration of polymers and plasticizer on in vitro drug release.
c) Characterization of prepared matrix transdermal patches.
d) The main objective of this transdermal dosage form is to deliver drug into systemic circulation at a predetermined rate with less side effects and skin irritation.

2. Material and Methods[8]

2.1 Selection of Drug and polymers

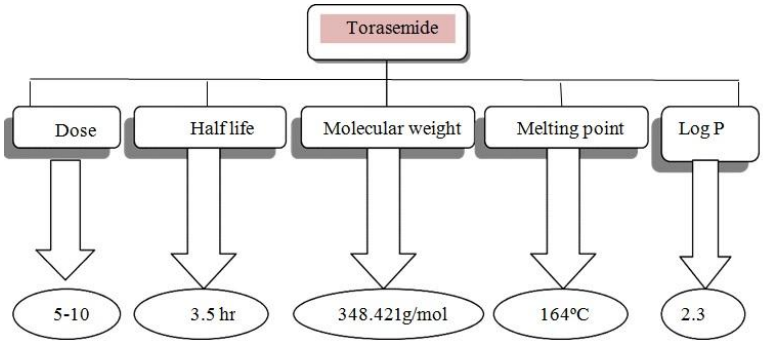
2.1.1 Selection of drug for Transdermal drug delivery:

- Drug should have a molecular weight less than approximately 1000 daltons. Drug should have affinity for both hydrophilic and lipophilic phases. An adequate solubility in lipid and water is necessary for better penetration of drug. (1mg/ml)
- The pH of the saturated solution should be in between 5-9.
- The potent drug with dose less than 10mg/day is desired
- The drug should have low melting point (<200ºC).
- Optimum partition coefficient is required for good therapeutic action.

2.1.2 Torasemide [9][10]

The suitability of torasemide with respect to dose, partition coefficient, biological half life, molecular weight was considered to be incorporated into matrix type transdermal delivery system.

Figure 1: Parameters considered for stability of torasemide



A) Selection of polymers for film formation

The blank polymeric films were formed using commonly film forming polymers using solvent evaporation technique. The detail composition of films is shown in table 1.

Table 1: Trial formulation for selection of polymer

Sr. No.	Polymer blends (500 mg)	Solvent(15 ml)	Plasticizer (30%)
1.	HPMC E15+EC(2:1)	methanol	Dibutylphthalate
2.	HPMC+ERS 100(3:2)	methanol	Dibutylphthalate
3.	HPMC+EC(3:2)	methanol	Dibutylphthalate
4.	HPMC+ERL100(3:2)	methanol	Dibutylphthalate
5.	ERS 100+ ERL100(3:2)	methanol	Dibutylphthalate
6.	ERL100+EC(9:1)	methanol	Dibutylphthalate
7.	ERS100+EC(9:1)	methanol	Dibutylphthalate
8.	HPMC+ERS 100(3:2)	Water: methanol(1:1)	PEG400
9.	HPMC+EC(3:2)	Methanol: water(1:1)	PEG400

Films were formed by solvent evaporation technique and visually inspected for its texture, uniformity in thickness and flexibility. Film No.11 was found to best for the said parameters which is then selected to prepare drug loaded film.

2.2 Preformulation study[11]

Preformulation testing is the first step in the rationale development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when in combined with excipients. The overall objective of the preformulation testing is to generate information useful to the formulator in developing stable and bio availability dosage forms which can be mass produced.

The goals of preformulation studies are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish it's compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies.

Description: The sample was evaluated visually for appearance, colour and odor.

Melting point: The melting point of drug was estimated with the help of melting point apparatus and compared with values given in literature.

2.3 Determination of partition coefficient

A] Calibration of drug in 7.4pH phosphate buffer and n-octanol Calibration of drug in 7.4 pH phosphate buffer using UV spectrophotometer

a) Preparation of 7.4 pH phosphate buffer:

0.2 M potassium dihydrogen phosphate: 0.2 M potassium dihydrogen phosphate prepared by adding 27.21 gm of potassium dihydrogen phosphate in distilled water and volume was made upto 1000ml.

0.2 M Sodium hydroxide: The 0.2 M NaOH was prepared by dissolving 4 gm of NaOH in distilled water and the volume was made up to 100 ml with distilled water. Place 50 ml 0.2M potassium dihydrogen phosphate in 200ml volumetric flask with 39.1ml of 0.2M NaOH solution and add distilled water to make the volume upto 1000ml to prepare 7.4 pH phosphate buffer.

The standard plot was developed as follows:

1. Torasemide (10 mg) was accurately weighed on an electronic weighing balance.
2. The weighed amount of Torasemide was dissolved in 5ml of methanol and volume was made up to 100 ml by 7.4 pH phosphate buffer using a volumetric flask to yield a stock solution containing 100µg/ml drug.
3. An appropriate aliquot portion of 0.2-1.4 ml of the above stock solution was transferred to separate 10ml volumetric flask and volume was made up with 7.4 pH phosphate buffer to obtain 2-14 µg/ml of GLB.
4. Samples were prepared in triplicate and absorbance was checked in UV Spectrophotometer at 284.5 nm wavelength against phosphate buffer as a blank

2.4 Solubility Studies[12]

The solubility studies were performed in phosphate buffer solution, pH 6.4 by adding excess amounts of drug in each case and keeping the excess drug containing phosphate buffer flasks on a water bath shaker NSW-133 for 24 h at 32°C. After 24 h, solutions were analyzed spectrometrically at 284.5 nm, which was the absorption maxima determined earlier and drug concentrations were calculated. The same study was done to determine solubility of drug in methanol.

2.5 Infrared spectroscopy

The potassium bromide (KBr) disks with Torasemide were prepared manually by press method. About 1 mg of drug was triturated with about 10 mg of dry KBr and then pressed into the pallet manually. Jasco FTIR-5300 was used to obtain IR spectra of the prepared disc of Torasemide. The scanning range was 4000-400 cm^{-1}. The spectrum was compared with that reported in literature.

2.6 Ultraviolet spectroscopy

The drug was standardized for its UV spectrum in methanol. Accurately weighed 10mg sample of Torasemide was dissolved in 10ml of methanol (HPLC grade), and the sample was suitably diluted to obtain 10µg/ml solution and scanned in the UV range from 200-400 nm on UV/Visible spectrometer against methanol as blank. The spectrum was compared with that reported in literature.

2.6.1 Analytical method development[13]:

Development of standard curve of the drug in methanol using UV- Spectrometer

The standard plot was developed as follows:

1. Torasemide (10 mg) was accurately weighed on an electronic weighing balance.
2. The weighed amount of Torasemide was dissolved in 5ml of methanol and volume was made up to 100ml using a volumetric flask to yield a stock solution containing 100µg/ml drug.
3. An appropriate aliquot portion of 0.2-1.4 ml of the above stock solution was transferred to separate 10ml volumetric flask and volume was made up with methanol to obtain 2-14 µg/ml of GLB.

3. Results and Discussion[14][16]

3.1 Preformulation study of Torasemide

Description: White crystalline powder and odorless.

Melting Point: Melting point was found to be 163.5ºC (Reported melting point 163.5ºC to 164.5ºC).

3.2 Determination of partition coefficient

Table 2: Partition coefficient of Torasemide

Partition coefficient of drug	Solvent system	Values
torasemide	Phosphate buffer –N-octanol	2.404

3.3 Solubility studies

The solubility of Torasemide was found to be very less as 78.94 ug/ml in phosphate buffer. The solubility of torasemide in methanol was found better than in pH 7.4 phosphate buffers.

Table 3: The solubility data

Solubility medium	Duration	Solubility (ug/ml)
Phosphate buffer 7.4	After 24 hr	49.03
Phosphate buffer 7.4	After 48 hr	78.94
Methanol	After 24 hr	77.85
Methanol	After 48 hr	92.21

3.3 Infrared spectroscopy

The IR spectrum of the drug recorded on Jasco FTIR-5300 spectrophotometer by KBr disk method (Figure 2). The result shows the presence of characteristic peaks as shown in which was compared with standard peaks. It was confirmed that the drug molecule was 1-Isopropyl-3-[(4-*m*-toluidino-3-pyridyl)sulfonyl]urea. a sharp peak corresponding to the N-H stretch, O-H stretch, C-H stretch, C-O, N-H, CH2, CH2 , C=O stretch, C-O aromatic C-H bands were observed at 3427 to 686cm−1, respectively as shown in Figure 2 and Table 4. Characteristic peaks of functional groups were observed in IR spectrum of excipients. So, identities of excipients were confirmed and no impurity was detected in the IR spectrum of excipients as shown in Figure 3. IR spectra of excipients and Drug showed no interaction as the major peaks of drug was observed in IR spectrum.

Figure 2: IR spectra of torasemide

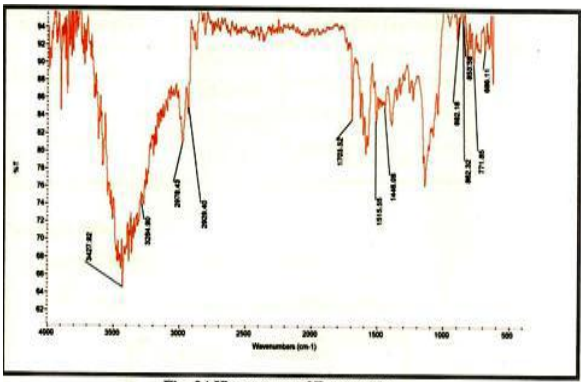


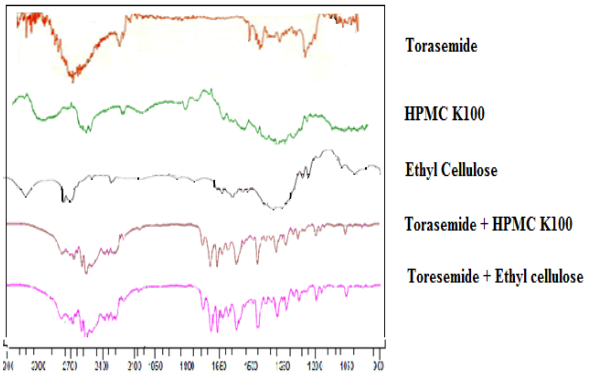
Table 4: Identification of functional group for Torasemide

IR frequency (cm-1)	Assignment
3427.42	N-H
3284.88	O-H
2978.31	C-H
1738.90	C-O
1528.53	N-H
1376.83	CH2 & CH2
882.18	=C-H & =CH2, NH2
771.85	O-H
686.11	C-H

3.4 Drug excipients compatibility study[17]

The FTIR analysis showed no change in endothermic peak of drug. The study indicated that there was no drug-excipient incompatibility/interaction. FTIR spectrum is shown as:

Figure 3: IR spectra of physical mixture of Torasemide with EC and HPMC



3.5 Formulation development

Part a: Formulation of trial batches

The transdermal films were formed and evaluated for physical imperfections. Physical appearance of the polymers (Ethyl cellulose and hydroxypropyl methyl cellulose) used for the fabrication of transdermal systems showed good film forming properties. The method adopted for casting the systems was found satisfactory.

Table 5: Formulation of trial batches

Sr. no	Polymer(mg)		Plasticizer (PEG- 400)	Drug (mg)
	HPMC	EC		
1	650 mg	300 mg	0.2 ml	160
2	650 mg	300 mg	0.3 ml	160
3	650 mg	300 mg	0.4 ml	160
4	700 mg	300 mg	0.2 ml	160
5	700 mg	300 mg	0.3 ml	160
6	700 mg	300 mg	0.4 ml	160
7	750 mg	250 mg	0.2 ml	160
8	750 mg	250mg	0.3 ml	160
9	750 mg	250mg	0.4 ml	160

Part b: Polymer selection of trial batches[18]:

HPMC and EC were used as a polymer in patch. All the films were transparent. All the trial Batches were formulated using various types and

proportion of polymer. When the concentration of polymer was increased, so drug release & appearance decrease.

Table 6: Polymer selection of trial batches

Formulation	Polymer Ratio	Appearance
F1	9:1	Film not form
F2	8:2	Flim sticky form
F3	7:3	Good film form
F4	6:4	Flim not form
F5	5:5	Average flim form

Part c: plasticizer variation of trial batches

PEG 400 and Glycerin were used as a Plasticizer in films. All the films were transparent. All the trial Batches were formulated using various types and proportion of plasticizer. Plasticizer also affects the film separation property of the film. When the concentration of Glycerin was increased, it also increases the flexibility of the film as compare to the PEG 400 films. Also Glycerin resulted in better film separation than PEG 400. Thus, it will be concluded that film separation could be improved in the presence of plasticizer Glycerin. The plasticizer affects the flexibility of the films hence folding endurance was also gets affected. The glycerin showed the good effect on folding endurance.

Table 7: Plasticizer variation of trial batches

Formulation	Plasticizer Ratio (PEG-400)	Appearance
F1	**0.1**	**Good**
F2	**0.3**	**Average**
F3	**0.5**	**Sticky**

3.6 Weight uniformity[19][20]

The weights of all transdermal patches were found to be uniform with their low standard deviation values. For each formulation, the weight of 3 patches was taken on a digital balance.

Table 8: Weight uniformity

Formulation code	Weight uniformity
F-1	0.0426
F-2	0.0336
F-3	0.0336
F-4	0.0333
F-5	0.0313
F-6	0.0210
F-7	0.0208
F-8	0.0203
F-9	0.0201

3.7 Tensile Strength: Tensile strength of the patch (Table 9) was calculated by using following formula,

$$TS = \frac{Break\ force}{a \times b} \times \frac{1+L}{l}$$

Where a, b and L are the width, thickness and length of the film and l is the elongation of film at break point

% Elongation = Final length - Initial length] ×100 /Initial length

Table 9: Tensile Strength

Formulation code	Tensile strength
F-1	2.13
F-2	3.30
F-3	3.88
F-4	2.96
F-5	3.27
F-6	3.41
F-7	2.89
F-8	3.21
F-9	3.34

3.8 Percent moisture absorption

The % moisture content was found to be between 4.52 to 2.45 (Table 10). The moisture content was found to increase with increasing concentration of hydrophilic polymers.

Table 10: Percent moisture absorption

Formulation Code	Percent moisture absoption
F1	2.45
F2	3.98
F3	6.97
F4	1.73
F5	3.63
F6	3.63
F-7	1.68
F-8	3.24
F-9	4.52

3.9 Preliminary trials for *vitro* drug release

In trial batches dissolution medium like 6.4 phosphate buffer used for the dissolution study of optimized M1 formulation. The cumulative % drug release of F1 to F5 formulation indicated the drug release in ph 6.4 phosphate buffer

Table 11: Preliminary trials for *vitro* drug release

Time	F1	F2	F3	F4	F5
0	0.00	0.00	0.00	0.00	0.00
30	4.22	7.04	2.81	1.40	0.89
45	13.57	14.07	10.37	7.29	4.38
60	20.09	22.00	15.20	13.04	10.52
120	28.77	30.42	23.03	20.61	16.58
180	36.28	39.25	30.43	29.30	23.11
240	54.93	48.77	38.17	36.94	31.06
360	73.37	60.38	46.45	45.22	39.34
420	95.25	76.86	60.38	57.35	49.91
480	94.29	75.71	68.51	59.73	

3.10 Effect of folding endurance on drug release profile: All the polymers were able to give the acceptable folding endurance values. The observed folding endurance was in the range of 50 to 250

Table 12: Effect of folding endurance on drug release profile

Formulation	Folding Endurance
F1	221
F2	202
F3	188
F4	173
F5	192

3.11 Optimization study

For the optimization of transdermal patches, the 32 factorial design was used using polymer ratio and penetration enhancer concentration as an independent variables. These formulations were prepared by same method and further evaluated.

Table 13: Cumulative % Drug Release of formulation

TIME (Min)					Cumulative % Drug Release				
F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0.25	5.63	1.40	1.14	2.56	2.17	2.94	7.04	4.99	4.99
0.5	10.87	7.29	8.66	10.32	9.74	8.98	12.48	7.93	7.93
0.75	17.12	11.63	12.73	16.44	16.54	14.85	17.45	14.96	14.96
1	25.19	16.13	17.65	21.80	22.20	19.96	24.22	21.48	20.09
2	31.31	23.80	23.22	29.08	29.44	26.98	31.62	29.01	27.09
3	37.11	29.10	30.49	35.44	35.87	35.50	38.72	35.55	34.61
4	45.66	35.54	36.73	41.36	42.76	40.17	47.53	42.69	41.69
5	54.56	40.81	44.30	47.97	50.62	47.63	59.66	53.17	50.81
6	63.28	48.21	53.10	56.35	58.26	54.33	69.15	64.77	62.38
7	67.06	67.06	66.08	73.56	72.08	78.89	82.13	82.77	79.38
8	82.64	82.64	79.99	93.75	91.32	87.54	97.62	96.12	94.13

3.12 Effects of folding endurance on optimized batch of in-vitro release

The observed folding endurance was in the range of to 50 to 250.

Table 14: Effects of folding endurance on optimized batch of *in-vitro* release

Formulation	Folding Endurance
F1	**179.00**
F2	**196.00**
F3	**227.00**
F4	**167.00**
F5	**188.00**
F6	**216.00**
F7	**164.00**
F8	**183.00**
F9	**207.00**

3.12 Kinetics of Drug Release[21][25]

In present study the dissolution were analyzed by PCP Disso Version 2.08 software to study the kinetics of drug release. The results showed that some of the formulations followed zero order kinetics and some followed peppas. The R2 value of all dissolution models is shown in Table 8.11 The value of n i.e. release exponent was found in the range of 0.70 to 0.95 From the mathematical treatment of the in vitro release data of Torasemide patch the values of R (coefficient of determination) has been obtained as presented in Table no 45. The values of n were obtained by the linear regression of log (Mt/M) vs. log t and were between 0.5 to 1 indicating non fickian diffusion or anomalous transport for all formulations. The best fit with the highest correlation r and determination ssR coefficients was shown by peppas model closely followed by the matrix model. None of the formulation followed first order model. All the formulations followed zero order model, except F1 F8 and F9 whose drug release conforms to peppas model.

Table 15: Dissolution kinetics (R values) of formulations F1 to F9

Formulation	Regression coefficient (R2)			Release exponent (n)		Best fit model
Zeo order	**First order**	**Matrix**		**Korsmeyer-Peppas**		**Hixon Crowell**
F1	0.9711	0.9723	0.9751	0.9875	0.9853	0.7088	Peppas
F2	0.9819	0.9205	0.9269	0.9626	0.9514	0.9547	Zero
F3	0.9876	0.9516	0.9448	0.9448	0.9731	0.9547	Zero
F4	0.9748	0.8635	0.9408	0.9625	0.9263	0.8366	Zero
F5	0.9781	0.8995	0.9512	0.9581	0.9581	0.8698	Zero
F6	0.9815	0.9221	0.9448	0.9771	0.9568	0.8308	Zero
F7	0.9833	0.8585	0.9612	0.9935	0.9421	0.7027	Zero
F8	0.9880	0.8729	0.9420	0.9893	0.9400	0.7995	Peppas

4. Conclusion

The Torasemide drug in the form of transdermal drug delivery system appeared to be promising as far as *In vitro* studies are concerned. This TDDS form can substantially reduce the dosing frequency and oral side effects of Torasemide as compared to its conventional dosage form. This transdermal patch will surely increase patient compliance due to its benefits over oral dosage forms. This system can be further explored for combination with other suitable drugs.

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