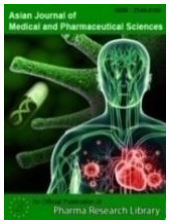

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Formulation and Characterization of Transferosome Transdermal Patch of Hydrochlorthizide

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A B S T R A C T

Hydrochlorothiazide transdermal patches offer a promising alternative to oral delivery, aiming for sustained therapeutic effects and improved patient compliance. Accurate drug quantification and stability within the formulation are essential for effective development. A UV-Visible spectrophotometric method was developed and validated to quantify Hydrochlorothiazide in pH 7.4 phosphate buffer, measuring absorbance at 229 nm. Compatibility between the drug and polymers was assessed using FTIR spectroscopy. Various transdermal patches were prepared via solvent casting and evaluated for thickness, weight uniformity, drug content, folding endurance, and tensile strength. In vitro drug release was monitored over 12 hours, and release kinetics were modeled to understand the drug release mechanism. Stability studies were conducted over three months under accelerated conditions. The spectrophotometric method showed strong linearity and precision. FTIR analysis confirmed the drug's stability in the polymer matrix. The patches demonstrated consistent physical and mechanical properties suitable for transdermal delivery. Drug release studies revealed sustained and near-complete release, fitting diffusion-controlled models, primarily the Korsmeyer-Peppas model. Stability tests indicated no significant changes in drug release profile or physical parameters over three months. Hydrochlorothiazide transdermal patches were successfully formulated with desirable mechanical strength, controlled drug release, and stability, suggesting their potential as an effective and patient-friendly therapeutic alternative.

Keywords: Hydrochlorothiazide, transdermal patch, UV-Visible spectrophotometry, FTIR, sustained drug release, drug stability, controlled release

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

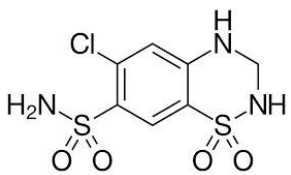

Fig.1: Hydrochlorothiazide

Molecular Formula: $C_7H_8ClN_3O_4S_2$
Molecular Weight: ~297.74 g/mol
IUPAC Name: 6-chloro-1,1-dioxo-3,4-dihydro-2H-1λ^6, 2, 4-benzothiadiazine-7-sulfonamide
Chem Spider ID: 34406
Density: ~1.6761 g/cm³ (estimated)
Boiling Point: ~577 °C (predicted)

Vapour Pressure: Not readily available due to low volatility
Flash Point: ~9 °C
Refractive Index: ~1.6100 (estimated)
Polar Surface Area: ~143 Å²
LogP (Octanol/Water): ~–0.07
Generic Name: Hydrochlorothiazide
Brand Names: Microzide, Hydrodiuril, Esidrix, Oretic, and others
Drug Category: Thiazide diuretic
Indications: Hypertension, edema due to heart failure, liver cirrhosis, or kidney disorders; also used in nephrogenic diabetes insipidus and calcium nephrolithiasis
Pharmacology: Inhibits sodium-chloride symporter in the distal convoluted tubule, promoting diuresis and reducing blood pressure
Potency: Moderate diuretic effect; effective at 12.5–50 mg/day
Tolerability: Generally well-tolerated; dose-dependent side effects
Contraindications: Anuria, hypersensitivity to sulfonamides, severe renal or hepatic impairment
Adverse Effects: Hypokalemia, hyponatremia, dizziness, hyperuricemia, photosensitivity, and rare allergic reactions
Availability: Widely available globally in oral tablet form, often in combination with other antihypertensives

2. Materials and Methods

Table 1: List of materials used

S.No	Materials	Source
1	Hydrochlorothiazide	Pharmatrain, Hyderabad
2	HPMC K15M	S.D. Fine chemicals, Mumbai
3	HPMC K100M	S.D. Fine chemicals, Mumbai
4	HPMC K200M	S.D. Fine chemicals, Mumbai
5	PVP K30	S.D. Fine chemicals, Mumbai
6	Tween 80	S.D. Fine chemicals, Mumbai
7	Sorbitol	S.D. Fine chemicals, Mumbai

Table 2: List of instruments/equipments used

S.No	Equipment's	Manufacturer/Supplier
1.	Electronic Balance module-AUW 2200	Shimadzu Corporation, Japan
2.	pH Meter	Metler Toledo, India
3.	UV-Visible Spectrophotometer (UV-1601), (UV-2550)	Shimadzu-Corporation, Japan.
6.	Dissolution Apparatus TDT-08L,	Electro lab, India.
8.	Vernier Caliper	Mitutoyo, Corps, Japan
9.	Disintegration tester (USP)	Electro Lab, India
10.	Hot air oven	Servewell instruments
11.	Sonicator	Sidilusonicator
12.	Gyratory shaker	Lab India.

Calibration curve of Hydrochlorothiazide in 7.4pH phosphate buffer:

a) Preparation of 7.4pH phosphate buffer:

50ml of 0.2M potassium dihydrogen orthophosphate solution was taken in a 200ml of volumetric flask, to which 22.4ml of 0.2M sodium hydroxide solution was added. Then volume was made up to the mark with distilled water and pH was adjusted to 7.4 with dilute sodium hydroxide solution [64].

b) Preparation of Hydrochlorothiazide standard stock solution (100µg/ml) in 7.4 pH phosphate buffer solution:

A standard stock solution of Hydrochlorothiazide was prepared by dissolving accurately weighed 10mg of Hydrochlorothiazide in 7.4pH phosphate buffer solution in a 100ml volumetric flask and the volume was made up to 100ml by using 7.4pH phosphate buffer solution to obtain a stock solution of 100µg/ml.

c) Determination of λmax of Hydrochlorothiazide:

From the standard stock solution, 1 ml was taken into 10ml volumetric flask. The volume was made up to 10ml with 7.4pH phosphate buffer solution. The resulting solution containing 10µg/ml was scanned between 200 and 400nm. The λmax was found to be 229nm and was used as analytical wavelength.

d) Calibration curve of Hydrochlorothiazide in 7.4pH phosphate buffer solution:

From stock solution, appropriate aliquots were pipette into different volumetric flasks and volumes were made up to 10 ml with 7.4pH phosphate buffer solution so as to get drug concentrations of 1,2,3,4 and 5µg/ml. The absorbencies of these drug solutions were estimated at λmax 229nm against a blank of 7.4pH phosphate buffer solution. This procedure was performed in triplicate to validate the calibration curve.

Fourier transform infrared radiation:

The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 $cm^{-1}$to 400 $cm^{-1}$by KBr pellet method.

Formulaton of Hydrochlorothiazide transdermal patches: Transdermal patches of Glipiside was prepared by solvent casting method. Take DCM and Ethanol in 1:1 ratio and dissolve the drug first. Then add the ingredients one by one and dissolve it properly in continuous stirring. The solutions were cast on to glass petri plate of 9 cm diameter and were dried in the oven at 70°C till a peelable film was formed. Then dried films were cut into rectangular shape pieces, with 4.0 cm^2 (2.0 cm × 2.0 cm) total surface area. Desired quantity of Glipiside was 10 mg (dose of drug) per 4.0 cm^2 films.

Stability studies:

In designing a dosage form it is necessary to know the inherent stability of the drug substance, to have an idea of what excipients to use, as well as how best to put them

together with the drug and to know that no toxic substance are formed. Limits of acceptability and therefore compromises must be reasonably defined. Because the measurements of these aspects of stability as well as determination of shelf life or expiration date for the final dosage form require long term stability studies for confirmation, they can be expensive and time consuming. Consequently it is necessary to define those study designs and conditions that show the greatest probability of success. The objective therefore of a stability study is to identify and help avoid or control situations where the stability of the active ingredient may be compromised.

Rationale for stability studies:

- There may be chemical degradation of active drug leading to a substantial lowering of the quantity of therapeutic agent in the dosage form.
- Although chemical degradation of the active drug may not be expensive, a toxic product may be formed in the decomposition process.
- Instability of drug product can lead to substantial lowering in the therapeutic efficiency of the dosage form.

Table 3: Stability Storage Conditions

Stability Storage Category	Testing schedule for Physical and Chemical attributes
LONG TERM 25°C ± 2°C / 60% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.
ACCELERATED 40°C ± 2°C / 75% ± 5% RH	1, 2, 3 & 6 Months
INTERMEDIATE 30°C ± 2°C / 60% ± 5% RH	3, 6, 9 & 12 Months
ZONE IV 30°C ± 2°C / 70% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.

3. Results and Discussion

Calibration curve of Hydrochlorothiazide in pH phosphate buffer solution: Standard calibration curve of Hydrochlorothiazide was drawn by plotting absorbance versus concentration. The λmax of Hydrochlorothiazide in 7.4pH phosphate buffer solution was found to be 229nm.

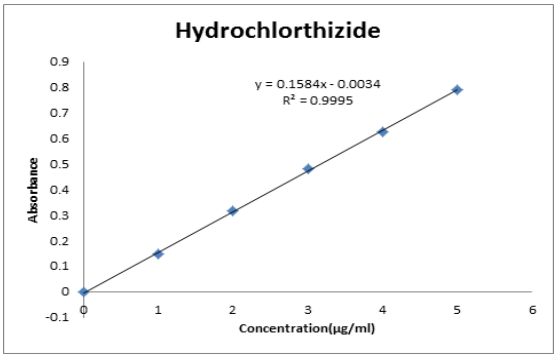

Fig.2: Standard calibration curve of Hydrochlorothiazide in 7.4pH phosphate buffer solution

Table 4: Calibration data of Hydrochlorothiazide in 7.4pH phosphate buffer at 229nm

Concentration (µg/ml)	Absorbance
0	0
1	0.147
2	0.314
3	0.481
4	0.624
5	0.789

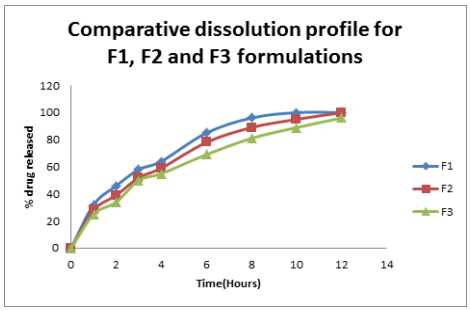

Fig.3: Comparative Dissolution profile for F1, F2 and F3 formulations

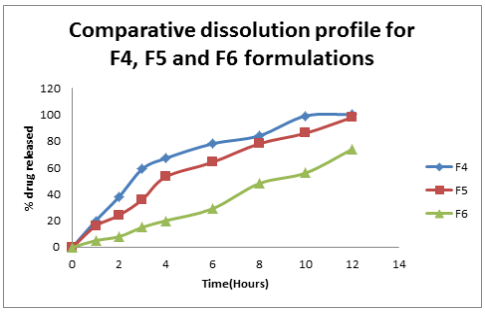

Fig.4: Comparative Dissolution profile for F4, F5 and F6 formulations

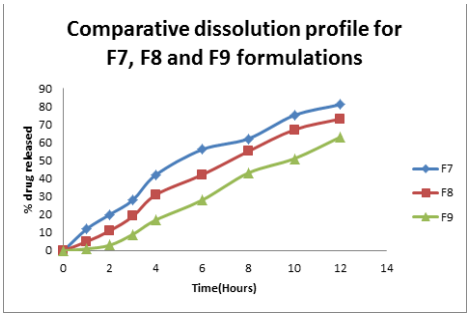

Fig.5: Comparative Dissolution profile for F7, F8 and F9 formulations

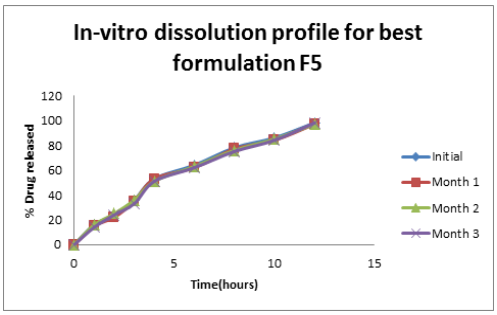

Fig.6: In-vitro release profile of F9 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

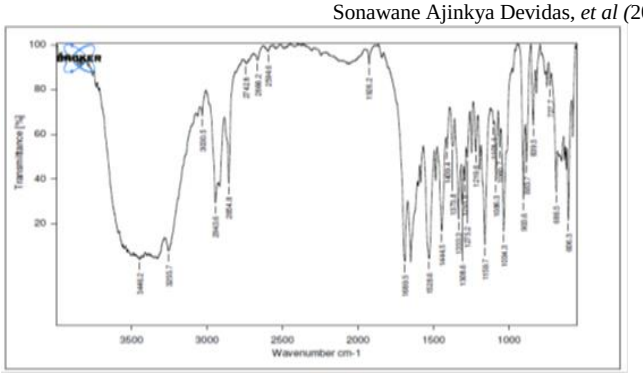

Fig.7: FTIR graph of Hydrochlorothiazide pure drug

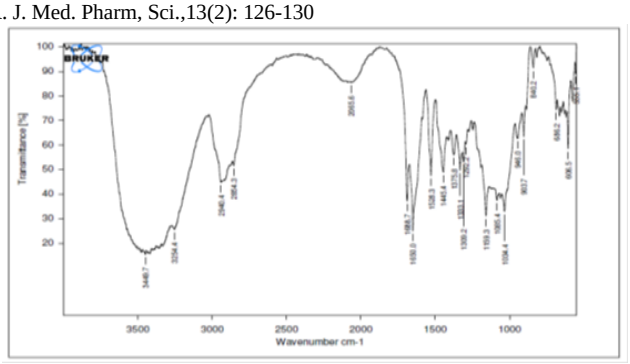

Fig.8: FTIR graph of Hydrochlorothiazide best formulation

Table 5: Evaluation parameters of Hydrochlorothiazide Transdermal patches

Formulation code	Thickness	Weight variation	Drug content	Folding endurance	Tensil strength
F1	162	Pass	98.23	201	2.74
F2	158	Pass	99.14	199	2.96
F3	153	Pass	99.67	212	3.12
F4	160	Pass	98.83	219	3.04
F5	157	Pass	99.37	210	2.83
F6	152	Pass	99.95	206	2.92
F7	147	Pass	99.67	218	3.15
F8	138	Pass	99.82	237	2.86
F9	156	Pass	99.37	204	2.46

Table 6: In-vitro drug release data for Transdermal patches

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	**0**	0	0	0	0
1	32	28	25	20	**16**	5	12	5	0
2	46	39	34	38	**24**	8	20	11	3
3	58	52	50	59	**36**	15	28	19	9
4	64	59	55	67	**53**	20	42	31	17
6	85	78	69	78	**64**	29	56	42	28
8	96	89	81	84	**78**	48	62	55	43
10	100	95	89	99	**86**	56	75	67	51
12	100	100	**96**	100	**98**	74	81	73	63

Table 7: R^2 and 'n' result table

Formulation code	R^2 Values				N Value
	Zero order	First order	Higuchi	Peppas	
F1	0.852	0.951	0.98	0.982	0.483
F2	0.9	0.986	0.992	0.991	0.535
F3	0.918	0.992	0.995	0.99	0.556
F4	0.869	0.84	0.973	0.94	0.624
F5	0.96	0.991	0.971	0.984	0.753
F6	0.988	0.964	0.867	0.989	1.113
F5	0.963	0.992	0.966	0.987	0.793
F6	0.987	0.99	0.926	0.986	1.103
F7	0.987	0.969	0.858	0.979	1.709

Table 8: *In-vitro* release profile of F5 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

Time (Hrs)	Initial	Month 1	Month 2	Month 3
0	0	0	0	0
1	16	15	16	14
2	24	22	25	24
3	36	35	36	33
4	53	53	51	51

6	64	62	63	62
8	78	77	76	75
10	86	84	85	84
12	98	97	97	98

4. Conclusion

A UV-Visible spectrophotometric method was developed and validated to quantify Hydrochlorothiazide in pH 7.4 phosphate buffer, recording maximum absorbance at 229 nm. The calibration curve showed a strong linear relationship between concentration and absorbance, confirming the method's reliability for routine quality control. Compatibility of Hydrochlorothiazide with polymers used in the patch formulation was established through FTIR analysis, which evidenced no significant interaction, thereby affirming drug stability within the patch matrix. Various transdermal patch formulations were prepared by solvent casting method using polymer blends, plasticizers, and permeation enhancers. These patches were evaluated for key physical parameters including thickness, weight uniformity, drug content, folding endurance, and tensile strength, which were found consistently within acceptable ranges indicating robust mechanical properties and uniform drug dispersion. In-vitro drug release studies demonstrated a sustained and near-complete release of Hydrochlorothiazide over a 12-hour period, with different formulations showing varied release profiles. Release kinetics favored diffusion-controlled mechanisms, particularly following the Korsmeyer-Peppas model, indicating controlled drug delivery suitable for maintaining therapeutic plasma levels. Stability studies on the optimized formulation confirmed that its physical properties and release profile remained consistent over three months under accelerated conditions, suggesting good shelf-life and formulation robustness. Overall, the study successfully developed Hydrochlorothiazide transdermal patches with effective mechanical integrity, controlled release, and drug stability, positioning them as a promising alternative to oral administration for better patient compliance and therapeutic efficacy.

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