CODEN [USA] : IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at : http://www.iajps.com Research Article

FORMULATION AND CHARACTERIZATION OF TRANSDERMAL DRUG DELIVERY SYSTEM OF AMILORIDE

Saleha[1], Dr Nazeemon[2]

[1] Student, Department of Pharmaceutics, Bharat Institute of Technology.

[2] Professor, Department of Pharmaceutics, Bharat Institute of Technology.

Abstract:

Objective: *This study aims to develop and evaluate transdermal drug delivery systems (TDDS) for Amiloride, a potassium-sparing diuretic, employing various polymers like HPMC K100M, Polyvinyl Alcohol and Polyvinylpyrrolidone to enhance drug delivery efficiency, control release, and improve patient compliance.*

Methods: *Several formulations of Amiloride transdermal patches were developed using different polymers, including hydrogels, polyurethanes, and acrylics. The formulations were characterized based on their physical properties (e.g., thickness, mechanical strength, adhesive properties), drug release kinetics, and skin permeation rates. In vitro release studies were conducted using Franz diffusion cells.*

Results: *The study successfully formulated Amiloride transdermal patches with various polymers, each influencing the drug release profile and adhesive properties differently. Optimal formulations demonstrated controlled and sustained release of Amiloride, with some polymers providing superior performance in drug permeability and release rate.*

Conclusion: *The developed transdermal systems showed promise in enhancing the delivery and efficacy of Amiloride through controlled release mechanisms. The choice of polymer significantly impacted the performance of the transdermal patches, suggesting potential for improved patient compliance and therapeutic outcomes.*

Keywords: Amiloride, HPMC K100M, Polyvinyl Alcohol and Polyvinylpyrrolidone

Corresponding Author:

Saleha,

Department of Pharmaceutics,
Bharat Institute of Technology
Mangalpally Village, Ibrahimpatnam Mandal
Telangana 501510
Mail Id: ***saleha9490@gmail.com***

QR code

Please cite this article in ***press Saleha*** *et al.,* ***Formulation And Characterization Of Transdermal Drug Delivery System Of Amiloride.,*** *Indo Am. J. P. Sci, 2024; 11 (09).*

INTRODUCTION:

Drug delivery system (DDS) is a generic term for a series of physicochemical technologies that can control delivery and release of pharmacologically active substances into cells, tissues and organs, such that these active substances could exert optimal effects [1, 2]. In other words, DDS covers the routes of administration and drug formulations that efficiently deliver the drug to maximize therapeutic efficacy while minimizing any side effect [3–5]. Depending on the delivery route, there are many types of administration modalities, such as oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection. Among them, the transdermal drug delivery system (TDDS) represents an attractive approach.

TDDS has become one of the most widely investigated routes of noninvasive drug delivery into the body through the skin, unlike conventionally used direct administration routes that make use of needle-based injections. TDDS has significantly influenced the delivery of various therapeutic agents, especially in pain management, hormonal therapy, and treatment of diseases of the cardiovascular and central nervous systems [6–9]. TDDS does not involve passage through the gastrointestinal tract; therefore, there is no loss due to first-pass metabolism, and drugs can be delivered without interference from pH, enzymes, and intestinal bacteria. In addition, TDDS can be used to control drug release according to usage restrictions, thereby contributing to the high persistence of this method. Most importantly, because TDDS is a noninvasive administration method and involves minimal pain and burden on the patient, drugs can be safely and conveniently administered to children or the elderly [10–12].

However, it still does not utilize its full potential due to the innate skin barrier. The skin is the outermost organ with a multi-layered structure, and the role of the skin is to protect our body by blocking environmental hazards such as chemicals, heat, and toxins [13, 14].

First, the skin barrier effect of the epidermis occurs in the stratum corneum, the outermost layer, and is a property of blocking external substances. The barrier effect is very significant in the transport of substances having a large molecular weight. In TDDS, it is generally accepted that the delivery of substances with small molecular weights utilizes the intracellular pathway. However, for substances having a large molecular weight, methods and various mechanisms using the intracellular pathway in addition to the intercellular pathway are introduced and used [15–17]. This is due to the structure of the skin because the part called lipid containing both cells and hydrophilic substances and hydrophobic substances does not have a perfectly regular position but exists with regularity [18]. These structural features can be explained by the principles of physicochemical properties that are attempted to enhance drug delivery through the skin. Next, the vascular system in the dermal layer can inhibit transdermal delivery. A one-cell-thick layer of endothelial cells terminating in the papillary loops of the superficial arteriovenous plexus near the dermal-epidermal junction in the upper dermis represents the interface between the tissues surrounding the skin and the human vasculature. The role of the endothelium in the skin is like that of the whole body. It actively responds to pressure, shear, osmotic pressure, heat, chemokines, and cytokines by modulating permeability and inducing vasodilation or constriction [19]. Therefore, the biggest issue of TDDS is to resolve the barrier effect of the stratum corneum, deliver the drug to the skin tissue, and pass through the cellular and vascular tissue to reach the target tissue. The problem is that only a small amount of the drug can be delivered through the skin tissue [20, 21].

The main aim of the project is to develop and evaluate a transdermal drug delivery system (TDDS) for Amiloride using various polymers to enhance drug delivery efficiency, control release, and improve patient compliance.

MATERIALS AND METHODS:

TABLE 1: LIST OF MATERIAL USED IN THE FORMULATION DEVELOPMENT11

Material	source
AMILORIDE	Procured From Sanofi Aventis Pharma, Ltd, India. Provided by **SURA LABS,** Dilsukhnagar, Hyderabad.
HPMC K100 M	Merck Specialities Pvt Ltd
Polyvinyl Alcohol	Merck Specialities Pvt Ltd
Polyvinylpyrrolidone	Merck Specialities Pvt Ltd
PEG-200(ml)	Merck Specialities Pvt Ltd
Dimethylsulphoxide(ml)	Merck Specialities Pvt Ltd
Methanol(ml)	Merck Specialities Pvt Ltd

METHODOLOGY:

Analytical method development:

A.UV scan:

A 100mg of Amiloride was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10µg/ml. 10µg/ml solution was scanned from 200-400nm.

B. Construction of calibration curve:

A 100mg of Amiloride was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 2,4,6,8and 10µg /ml. The absorbance's of these solutions were determined spectrophotometrically at 284 nm.

Pre formulation study

A. Colour, Odour, Taste and Appearance:

The drug sample was evaluated for its Colour, odour and appearance.

B. Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus.

C. Determination of solubility:

The solubility of Amiloride was determined by adding excess amount of drug in the solvent. The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.

Saturated solution of Amiloride prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 280 nm and 284 nm for phosphate buffer and distilled water respectively.

Formulation of transdermal patches

Preparation of blank patches:

Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Formulation of drug incorporated transdermal patches:

The matrix-type transdermal patches containing Amiloride were prepared using different concentrations of HPMC K100 M, Ethyl Cellulose and Polyvinylpyrrolidone. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Dimethylsulphoxide was used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch. The formulation table is given in table no. 2.

Table 2: Formulation of Amiloride patches

INGREDIENTS	FORMULATION CHART								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Amiloride	5	5	5	5	5	5	5	5	5
HPMC K100 M	5	10	15	-	-	-	-	-	-
Ethyl Cellulose	-	-	-	5	10	15	-	-	-
Polyvinylpyrrolidone	-	-	-	-	-	-	5	10	15
PEG-200(ml)	10	10	10	10	10	10	10	10	10
Dimethylsulphoxide(ml)	5	5	5	5	5	5	5	5	5
Methanol(ml)	15	15	15	15	15	15	15	15	15

Evaluation parameters of patches
Physical evaluations
a. Thickness

The thickness of patches was measured by digital Verniers calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

b. Folding endurance

The folding endurance was measured manually for the prepared patches. A strip of patch (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

c. Weight variation
The three disks of 2*1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

d. Drug content Determination

The prepared drug contained patches specified surface area (2 cm^2) were cut and dissolved in (5% of methanol contained) 100ml of pH 7.4 phosphate buffer, and vigorously shaked for 12hrs, and then sonicated for 15 minutes, centrifuged at 5000 rpm for 30 min. Filter the drug contained polymeric solution through 42 number whatmann filter paper, then 1ml of the filtrate was taken in a test tube and dilute it for five times with same solvent by using double beam Uv-Visible spectrophotometer to determined drug content at λmax 284 nm. Respected Placebo patch was taken as a blank solution.

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = I1 - I2 \text{ X } 100$$

I2 = Final length of each strip
I1 = Initial length of each strip

***In-vitro* drug diffussion study:**
The *in vitro* study of drug permeation through the semi permeable membrane was performed using a Franz type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 37±0.5ºC. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 284 nm.

Drug release kinetics:

Diffusion data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero-Order Kinetics:

Zero order as cumulative amount of Percentage drug released vs. time

$$C=K0t$$

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First order kinetics:

First order as log cumulative percentage of log (%) cumulative drug remaining vs time,

$$L o g C = L o g C o - k t / 2.303$$

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi model:

Higuchi's model as cumulative percentage of drug released vs square root of time

$$Q = K t 1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Kors meyer Peppas equations:

Korsmeyer peppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet. Log cumulative percentage of drug released VS Log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M\infty=Ktn$$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

Compatibility study

FTIR study:

The infrared spectrum of the pure Amiloride n sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

RESULTS AND DISCUSSION:

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

Analysis of drug:

A. UV scans:

The lambda max of Amiloride was found to be 284 nm.

B. construction of calibration curve:

Table 3: Standard graph of Amiloride

Concentration (µg/ml)	Absorbance (at 284 nm)
0	0
2	0.109
4	0.215
6	0.316
8	0.419
10	0.522

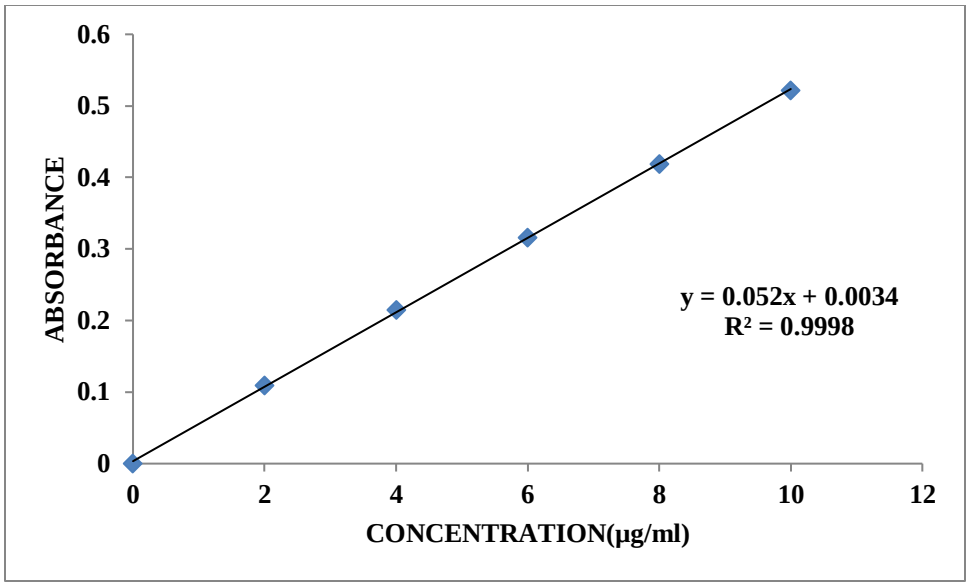

Figure 1: Standard calibration curve of Amiloride

Pre formulation study

Totally, Nine formulation trials were done with the aim to achieve the successful matrix type Amiloride transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

A. Colour, odour, taste and appearance

Table 4: Results of identification tests of drug

Parameter	Amiloride
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

B. Melting point determination:

Table 5: Results of melting point determination tests of drug

Drug	**Reported melting point**
Amiloride	240 °C

C. Determination of solubility:

Table 6: Solubility Determination

solvent	**Drug solubility(mg/ml)**
Distilled water	4.93
Ph 7.4 phosphate buffer	78.3

Evaluation of Patch

The formulations A1 to A9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 1.047±0.001 to 1.051±0.004 mm.

All formulations from A1 to A9 shows weight variation in between 80 ±9.58 to 89 ±4.69 mg.

Folding endurance from formulations A1 to A9was found to be in between 90 ± 1.84 to 99 ± 2.15 which can withstand the folding of the skin.

All formulations showed % drug content from 96.2 ± 3.87 to 99.74 ± 1.57.

Table 7: Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug Content
A1	85±1.05	1.046 ± 0.003	91 ± 0.15	100	Transparent	98.1 ± 2.10
A2	88 ±5.36	1.049±0.008	96 ± 1.39	99	Transparent	97.28 ± 0.45
A3	81 ±2.84	1.051±0.004	95 ± 2.26	100	Transparent	98.69 ± 2.21
A4	85 ±5.41	1.041±0.009	90 ± 1.84	100	Transparent	99.1 ± 2.61
A5	87 ±9.18	1.049±0.004	92 ± 3.10	99	Transparent	96.2 ± 3.87
A6	89 ±4.69	1.041±0.007	99 ± 2.15	100	Transparent	97.35 ± 0.59
A7	80 ±9.58	1.047±0.001	94 ± 2.36	99	Transparent	98.11 ± 2.34
A8	86 ±3.86	1.045±0.009	97 ± 2.04	100	Transparent	99.74 ± 1.57
A9	88±2.74	1..044±0.008	98±2.17	99	Transparent	98.22± 1.88

***In vitro* diffusion study:**

All the formulation *in vitro* diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5 ºC. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 8: *In vitro* drug permeation of Amiloride

Time (hr)	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	0	
1	13.30	24.43	16.73	21.63	24.94	19.52	18.94	19.29	18.21
2	21.26	31.04	21.92	28.84	28.28	25.93	22.76	26.91	29.43
3	25.74	34.98	28.04	34.42	38.78	36.57	24.65	29.26	34.11
4	34.98	38.09	34.76	49.28	47.37	41.82	33.04	37.15	41.68
5	43.65	46.92	41.21	51.13	54.78	46.65	36.85	44.68	48.72
6	48.48	57.88	52.47	67.71	63.13	53.21	40.01	55.89	57.41
7	55.74	58.43	58.65	74.99	68.21	61.92	51.76	63.62	65.62
8	61.53	68.15	64.85	78.16	78.85	67.67	56.52	69.23	69.89
9	67.31	77.65	72.57	85.05	82.37	74.29	64.23	76.75	73.92
10	72.85	79.94	76.69	89.27	88.71	83.72	73.51	84.43	82.24
11	75.12	81.02	82.36	94.13	93.25	91.36	81.25	87.59	89.61
12	81.81	86.51	88.42	99.92	97.12	96.97	91.18	93.22	95.63

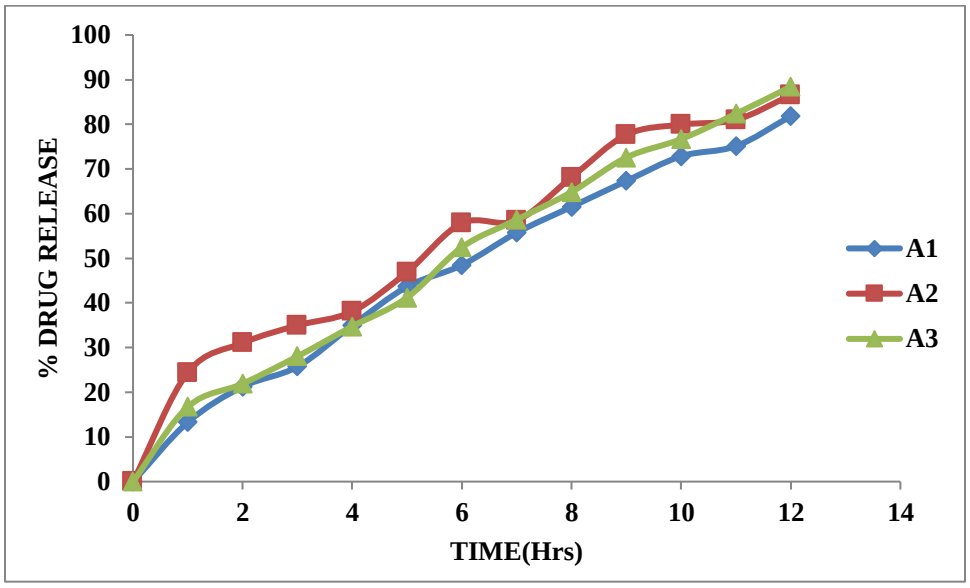

Figure 2: Cumulative % drug permeation of Amiloride patch (A1 to A3)

The formulations A1 to A3 were prepared by different concentrations of HPMC K100 M (5,10,15mg in 2*2 cm^2patch, the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration the drug permeation is more within 12 hours it was total amount of drug was permeated. The 15mg concentration of polymer was showed maximum drug released at 12 hrs. 88.42%. Hence in that 3 formulations showed total drug release at desired time period.

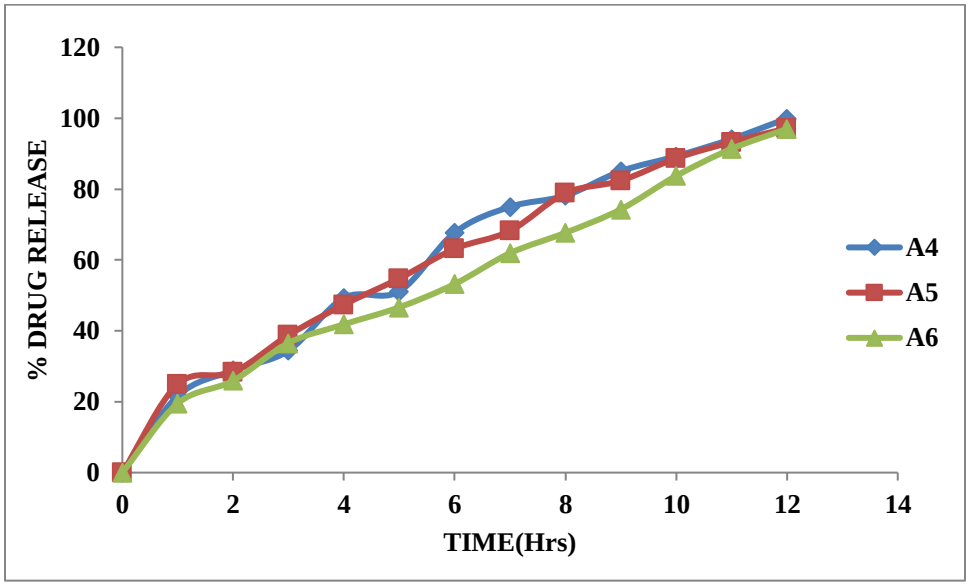

Figure 3: Cumulative % drug permeation of Amiloride patch (A4 to A6)

The formulations A4to A6were prepared by different concentrations of Polyvinyl Alcohol (5, 10, and 15) in 2*2 cm^2 patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 10mg (A4) concentration of polymer was showed maximum drug release 99.92 within 12 hours.
The 15mg (A4) concentration of polymer was showed maximum drug released at 12 hours 99.92%.

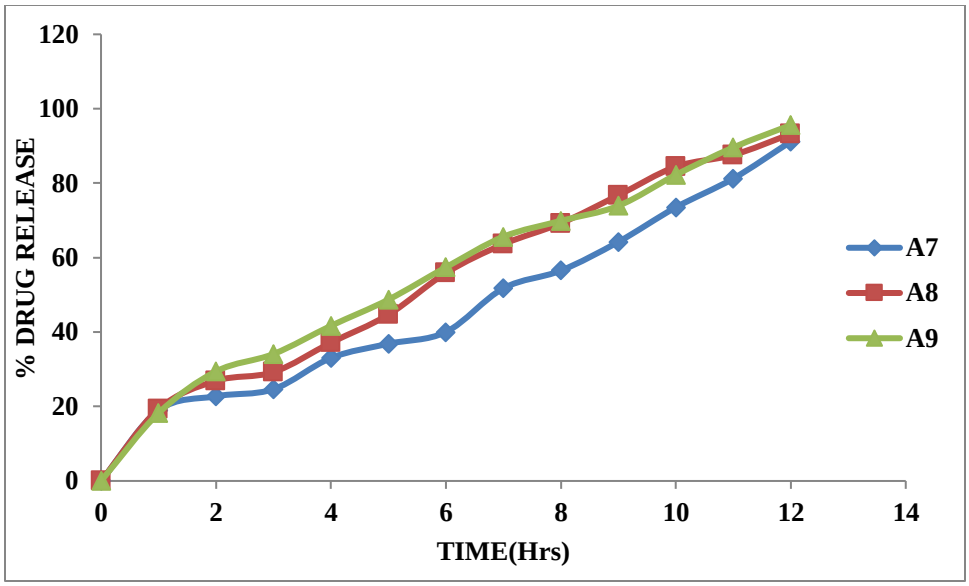

Figure 4: Cumulative % drug permeation of Amiloride patch (A7 to A9)

The formulations A7to A9 were prepared by different concentrations of Polyvinylpyrrolidone (5, 10, and 15mg) in 2*2 cm^2 patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 15mg (A9) concentration of polymer was showed maximum drug release 95.63 within 12 hours. The 15mg (A9) concentration of polymer was showed maximum drug released at 12 hours 95.63%.

Among all 9 formulations A4 formulation showed good drug permeation from the patch.
Among all *in vitro* evaluation parameters A4 formulation passed all evaluation parameters.

Kinetic models for Amiloride

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 9: Kinetics data of A4 Amiloride patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
21.63	1	1.000	1.335	0.000	1.894	21.630	0.0462	-0.665	78.37	4.642	4.279	0.362
28.84	2	1.414	1.460	0.301	1.852	14.420	0.0347	-0.540	71.16	4.642	4.144	0.498
34.42	3	1.732	1.537	0.477	1.817	11.473	0.0291	-0.463	65.58	4.642	4.033	0.609
49.28	4	2.000	1.693	0.602	1.705	12.320	0.0203	-0.307	50.72	4.642	3.702	0.940
51.13	5	2.236	1.709	0.699	1.689	10.226	0.0196	-0.291	48.87	4.642	3.656	0.986
67.71	6	2.449	1.831	0.778	1.509	11.285	0.0148	-0.169	32.29	4.642	3.184	1.457
74.99	7	2.646	1.875	0.845	1.398	10.713	0.0133	-0.125	25.01	4.642	2.924	1.717
78.16	8	2.828	1.893	0.903	1.339	9.770	0.0128	-0.107	21.84	4.642	2.795	1.846
85.05	9	3.000	1.930	0.954	1.175	9.450	0.0118	-0.070	14.95	4.642	2.463	2.178
89.27	10	3.162	1.951	1.000	1.031	8.927	0.0112	-0.049	10.73	4.642	2.206	2.436
94.13	11	3.317	1.974	1.041	0.769	8.557	0.0106	-0.026	5.87	4.642	1.804	2.838
99.92	12	3.464	2.000	1.079	-1.097	8.327	0.0100	0.000	0.08	4.642	0.431	4.211

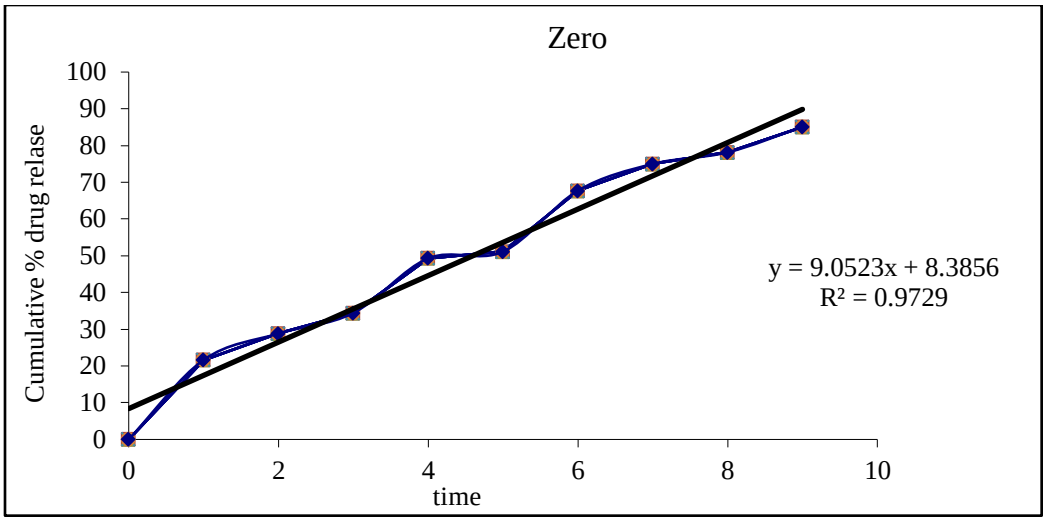

Figure 5: Graph of Zero order kinetics

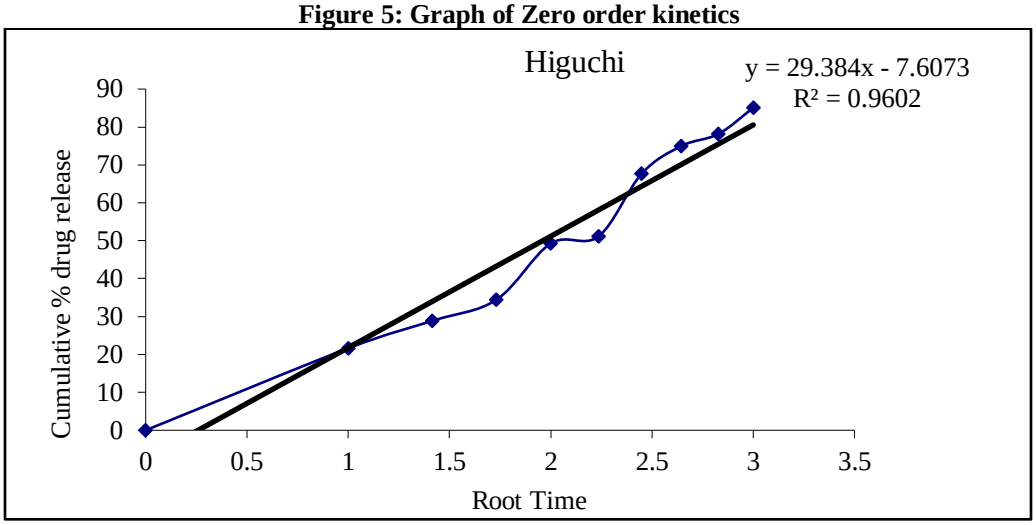

Figure 6: Graph of Higuchi release kinetics

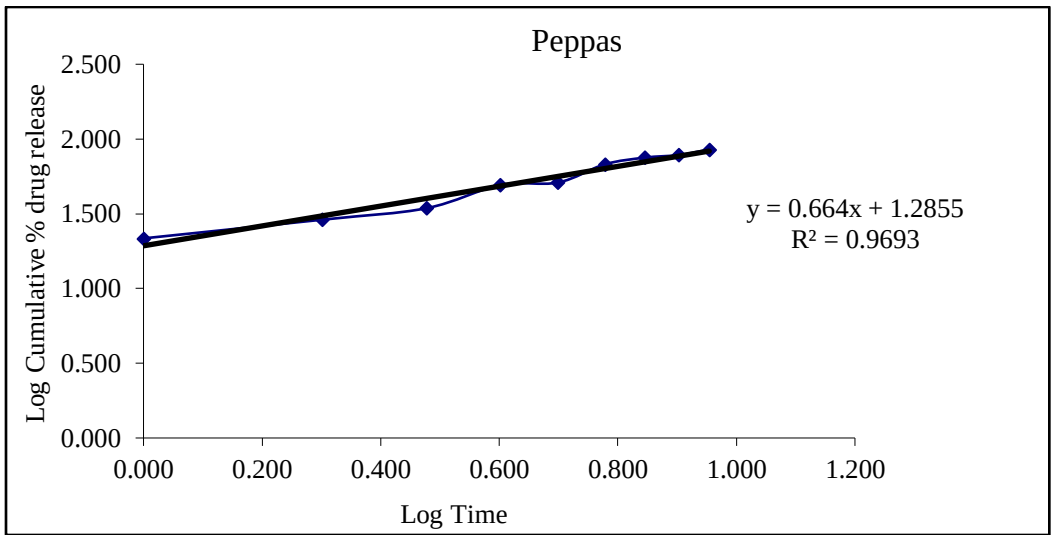

Figure 7: Graph of peppas release kinetics

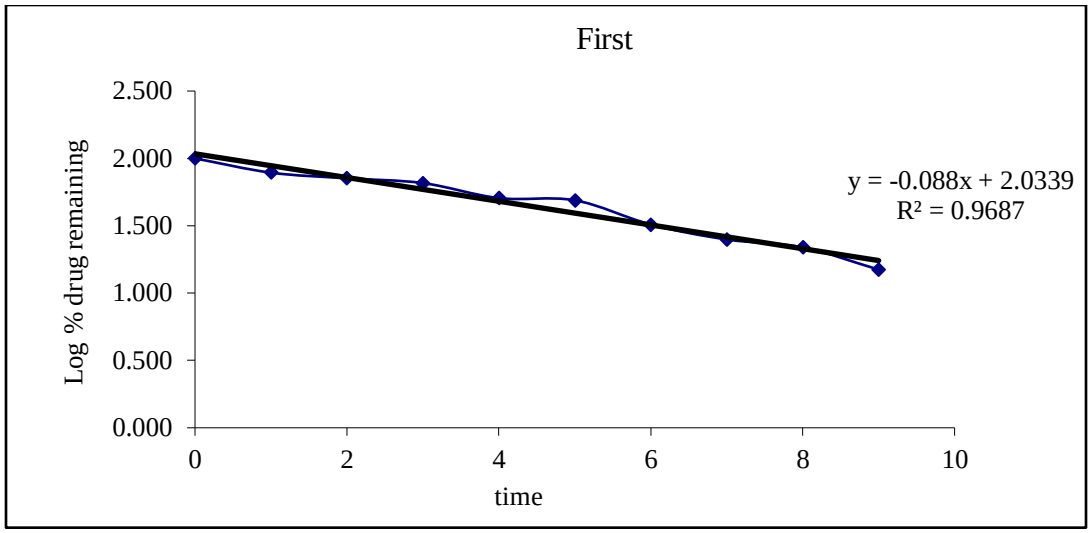

Figure 8: Graph of First order release kinetics

From the above data the optimized formulation followed Zero order model rule.

Compatibility studies:

IR SPECTROSCOPY:

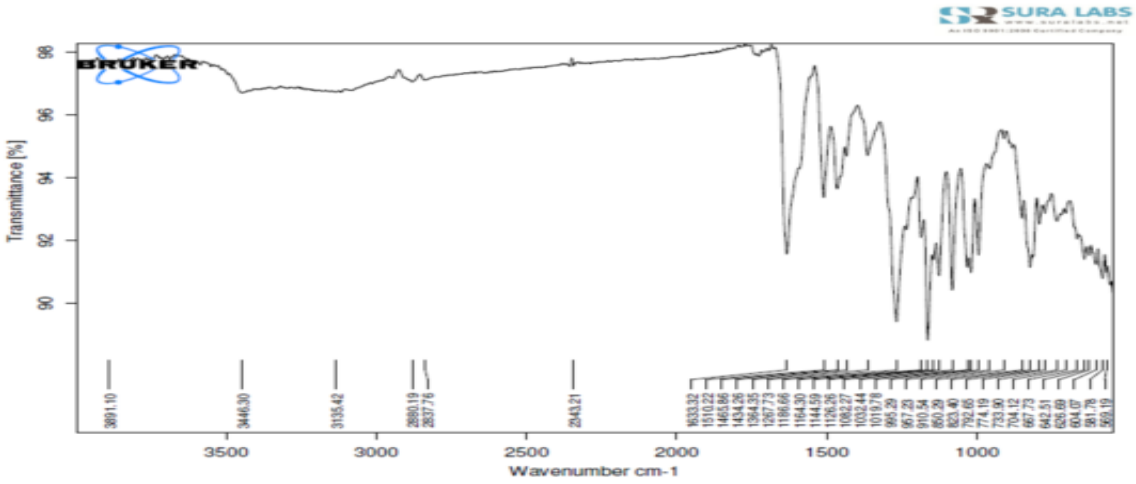

Figure 9: FTIR Spectrum of pure Amiloride drug

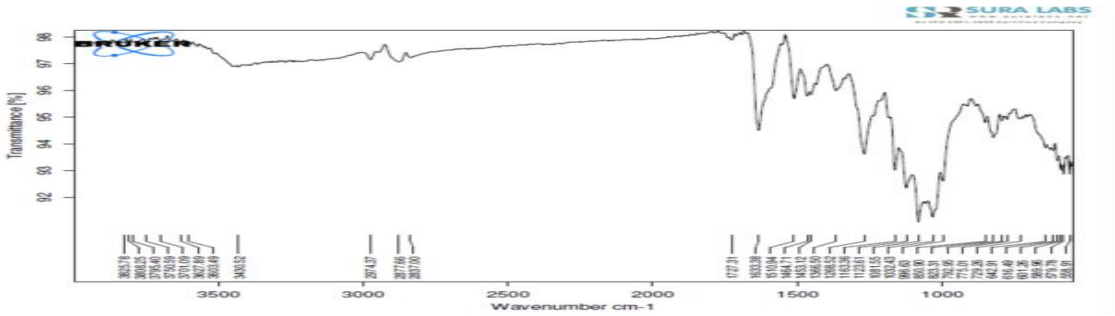

Figure 10: FTIR of Optimized formulations

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

CONCLUSION:

The formulation and characterization of a transdermal drug delivery system (TDDS) for Amiloride utilizing various polymers have demonstrated promising outcomes with respect to enhancing drug delivery efficiency and patient compliance. The key findings and conclusions are as follows:

1. **Successful Formulation:**
   - Various polymers were successfully to develop Amiloride transdermal patches, each contributing differently to the overall properties of the patches. The formulations were designed to optimize drug release and skin adhesion properties.
2. **Characterization Results:**
   - **Physical Properties:** The formulated patches exhibited acceptable physical characteristics including uniform thickness, adequate mechanical strength, and satisfactory adhesive properties. The polymer choice significantly influenced these properties.
   - **Drug Release:** In vitro release studies indicated that the selected polymers controlled the release of Amiloride in a sustained manner, with some formulations showing a more favorable release profile, suggesting potential for enhanced therapeutic efficacy.

REFERECES:

1. Vega-Vásquez P, Mosier NS, Irudayaraj J. Nanoscale drug delivery systems: from medicine to agriculture. *Front Bioeng Biotechnol*. 2020;8:79. doi: 10.3389/fbioe.2020.00079. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021. 10.1038/s41551-021-00698-w. [PubMed]
3. Mali AD, Bathe R, Patil M. An updated review on transdermal drug delivery systems. *Int J Adv Sci Res*. 2015;1(6):244–254. doi: 10.7439/ijasr.v1i6.2243. [CrossRef] [Google Scholar]
4. Li C, Wang J, Wang Y, Gao H, Wei G, Huang Y, Yu H, Gan Y, Wang Y, Mei L, Chen H, Hu H, Zhang Z, Jin Y. Recent progress in drug delivery. *Acta Pharm Sin B*. 2019;9(6):1145–1162. doi: 10.1016/j.apsb.2019.08.003. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
5. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: An overview. *Int J Pharm Sci Rev Res*. 2010;3(2):49–54. [Google Scholar]
6. Roohnikan M, Laszlo E, Babity S, Brambilla DA. Snapshot of transdermal and tropical drug delivery research in Canada. *Pharmaceutics*. 2019;11(6):256. doi: 10.3390/pharmaceutics11060256. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Peña-Juárez MC, Guadarrama-Escobar OR, Escobar-Chávez JJ. Transdermal delivery Systems for Biomolecules. *J Pharm Innov*. 2021;6:1–14. [PMC free article] [PubMed] [Google Scholar]
8. Ali H. Transdermal drug delivery system & patient compliance. *MOJ Bioequiv Availab*. 2017;3(2):47–48. [Google Scholar]
9. Leppert W, Malec–Milewska M, Zajaczkowska R, Wordliczek J. Transdermal and Topical Drug Administration in the Treatment of Pain. *Molecules*. 2018;23(3):681. doi: 10.3390/molecules23030681. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Akhter N, Singh V, Yusuf M, Khan RA. Non-invasive drug delivery technology: development and current status of transdermal drug delivery devices, techniques and biomedical applications. *Biomed Tech*. 2020;65(3):243–272. doi: 10.1515/bmt-2019-0019. [PubMed] [CrossRef] [Google Scholar]
11. Pires LR, Vinayakumar KB, Turos M, Miguel V, Gaspar J. A perspective on microneedle-based drug delivery and diagnostics in Paediatrics. *J Pers Med*. 2019;9(4):49. doi: 10.3390/jpm9040049. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
12. Ruby PK, Pathak SM, Aggarwal D. Critical attributes of transdermal drug delivery system (TDDS) – a generic product development review. *Drug Dev Ind Pharm*. 2014;40(11):1421–1428. doi: 10.3109/03639045.2013.879720. [PubMed] [CrossRef] [Google Scholar]
13. Ali S, Shabbir M, Shahid N. The structure of skin and transdermal drug delivery system - a review. *Res J Pharm Tech*. 2015;8(2):103–109. doi: 10.5958/0974-360X.2015.00019.0. [CrossRef] [Google Scholar]
14. Wang M, Luo Y, Wang T, Wan C, Pan L, Pan S, He K, Neo A, Chen X. Artificial skin perception. *Adv Mater*. 2020;33:e2003014. doi: 10.1002/adma.202003014. [PubMed] [CrossRef] [Google Scholar]
15. Hutton AR, McCrudden MT, Larrañeta E, Donnelly RF. Influence of molecular weight on transdermal delivery of model macromolecules using hydrogel-forming microneedles: potential

to enhance the administration of novel low molecular weight biotherapeutics. *J Mater Chem B*. 2020;8(19):4202–4209. doi: 10.1039/D0TB00021C. [PubMed] [CrossRef] [Google Scholar]

16. Andrews SM, Jeong EH, Prausnitz MR. Transdermal delivery of molecules is limited by full epidermis, Not Just Stratum Corneum. *Pharm Res*. 2013;30(4):1099–1109. doi: 10.1007/s11095-012-0946-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Chaulagain B, Jain A, Tiwari A, Verma A, Jain SK. Passive delivery of protein drugs through transdermal route. *Artif Cells Nanomed Biotechnol*. 2018;46(1):472–487. doi: 10.1080/21691401.2018.1430695. [PubMed] [CrossRef] [Google Scholar]
18. Uchechi O, Ogbonna J, Attama AA. *Application of nanotechnology in drug delivery*. Sezer AD: InTech C; 2014. Nanoparticles for dermal and transdermal drug delivery; pp. 193–235. [Google Scholar]
19. Zhou X, Hao Y, Yuan L, Pradhan S, Shrestha K, Pradhan O. Nano-formulations for transdermal drug delivery: a review. *Chin Chem Lett*. 2018;29(12):1713–1724. doi: 10.1016/j.cclet.2018.10.037. [CrossRef] [Google Scholar]
20. Kováčik A, Kopečná M, Vávrová K. Permeation enhancers in transdermal drug delivery: benefits and limitations. *Expert Opin Drug Deliv*. 2020;17(2):145–155. doi: 10.1080/17425247.2020.1713087. [PubMed] [CrossRef] [Google Scholar]
21. Pawar PM, Solanki KP, Mandali VA. Recent advancements in transdermal drug delivery system. *Int J Pharm Clin Res*. 2018;10(3):65–73. [Google Scholar]