RESEARCH ARTICLE

Formulation Development and Evaluation of Transdermal Patches of Apigenin

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Received: 25th March, 2024; Revised: 08th July, 2024; Accepted: 04th August, 2024; Available Online: 25th September, 2024

ABSTRACT

Apigenin is a flavonoid that is abundantly present in fruits and vegetables. It has a diverse range of therapeutic properties, including cardioprotective, neuroprotective, analgesic, and cancer-preventive effects. Its safety profile, even at higher doses, makes the compound particularly valuable. Apigenin, along with excipients, was used to formulate patches using the solvent-casting method on a glass mold. Seven distinct batches of patches were formulated using different combinations of polymers. The drug-polymer ratios employed in these formulations were (1:2), (1:3), (1:4), (1:4), (1:(2:8), (1:(1:9), and (1:(2:8) for both drugs. The formulated patches were evaluated and results indicate that the transdermal patches (TP5) have promising results.

Keywords: Apigenin, Transdermal patches, Formulation, Evaluation, Solvent casting.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.3.14

How to cite this article: Tirkey F, Dwivedi A. Formulation Development and Evaluation of Transdermal Patches of Apigenin. International Journal of Drug Delivery Technology. 2024;14(3):1353-1356.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The transdermal drug delivery system is an innovative and promising approach. It offers several advantages, such as controlled release, enhanced bioavailability, fewer side effects and patient compliance. However, there are several limitations, such as drug loading capacity and the presence of a skin barrier that limits the use of TDDS. Ongoing development and research are focused on providing novel approaches, such as nanoparticles and vesicles, that can expand the use of TDDS further, overcoming existing limitations and ushering in a new era of efficient and patient-friendly drug administration.[1]

Transdermal patches are an example of advancements in the drug delivery system, offering numerous advantages such as controlled release, ease of administration, and reduced side effects. They have narrowed the gap between therapeutic efficacy and patient compliance. However, as they continue to evolve, several limitations must be addressed. Ongoing research aims to provide innovative solutions for the current limitations of this dosage form, indicating a promising future for transdermal patches in the pharmaceutical and health industries. Any drug delivery system is designed for the purpose of delivering the desired amount of drug and maintaining the desired concentration of drug (therapeutic concentration) at a desired site in the body for the desired action. Controlled release of drug over a specific duration within the body is also desired from the therapeutics.[2]

Apigenin is a flavonoid that is abundantly present in fruits and vegetables. It has a diverse range of therapeutic properties, including cardioprotective, neuroprotective, analgesic, and cancer-preventive effects. Its safety profile, even at higher doses, makes the compound particularly valuable. Widely accepted as a nutraceutical, it is well-tolerated in humans. However, novel technologies can be employed to enhance the compound's efficacy. Future research should explore innovative formulations to optimize efficacy and establish sustainable techniques for extracting flavonoids from natural sources.[3]

MATERIAL AND METHODS

Selection of Drug and Excipients

Apigenin drug was selected for the present study after thoroughly going through the literature. After checking various compatibility parameters, Span 80, propylene glycol, ethyl cellulose and HMPC E5 are selected as excipients for the present study.

Formulation of Matrix-type Transdermal Patches

The solvent casting method was employed for casting matrix patches on a glass mold. Numerous polymer patches were developed by incorporating drugs. [4]

Formulation of Transdermal Patches

The solvent casting method was employed for casting patches on a glass mold. Seven different variants of polymer patches were developed. Only HPMC E5 was used for the development of the first 3 formulations. Drug vs polymer ratio was taken as 1:2, 1:3 and 1:4 for TP1, TP2 and TP3 formulations, respectively. DMSO was used as a solvent in these preparations.

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Table 1: Composition of an matrix-based TP

Ingredients	*TP1 (1:2)*	*TP2 (1:3)*	*TP3 (1:4)*	*TP4 (1:4)*	*TP5 [(1:(2:8)]*	*TP6 [(1:(1:9)]*	*TP7 [(1:(2:8)]*
Drug (AN) [mg]	70	70	70	70	70	70	70
HPMC- E5 [mg]	140.0	210.00	280.00	280.00	140.00	70.00	140.0
Ethyl cellulose [mg]	-	-	-	-	560.00	630.00	560.00
Span 80 (%) [mg]	-	-	-	1.0	-	-	1.0
PEG (%) [mg]	3.0	3.0	3.0	3.0	3.0	3.0	3.0

TP4 was formulated by using Span 80 as a permeation enhancer at 1% concentration, along with ethyl cellulose. Drug polymer ratio was taken as 1:4. In TP5 and TP6, propylene glycol and HPMC E5 were used in combination with drug polymer ratio as [1:(2:8)] and [1:(1:9)], respectively. MeOH and $CHCl_3$ were taken as solvents in TP5 and TP6 formulations at 1:1 ratio. TP7 was formulated by using HPMC E5 and ethyl cellulose with span80 and permeation enhancer as mentioned in Table 1. These were used at a ratio [1:(2:8)]. PEG was also taken in TP7 as a plasticizer.

Evaluation of the Formulated Transdermal Patches[5-7]

Physical appearance

Every patch was visually inspected for parameters such as smoothness, flexibility, bubble entrapment, clarity and color. These properties play an important role in the determination of the acceptability of therapeutics by patients.

Thickness

A digital thickness gauge developed in Japan was used for the determination of the thickness of transdermal patches. The average thickness was taken for four readingss from different points as 2cm by 2cm.

Weight variation

About 10 randomly selected patches were weighed on balance and the mean weight was calculated. It was then calculated for each patch and the average weight variation was taken for the stud.

Flatness

About 5 patches were selected on a random basis. The longitudinal length of each strip was measured. Difference due to variation in length was measured.

Folding endurance

Folding endurance for a transdermal patch can be defined as the number of times a patch can be folded before it develops and visible cracks or breaks. It signifies the stability of the patch and the force it can withstand during folding due to the brittle character of the patch. Folding endurance was determined by folding the patch at the same location several times before it developed any visible cracks or breaks.

Tensile strength

The developed patches' mechanical properties were measured by evaluating their tensile strength. Using self-designed assembly, the patches' tensile strength will be ascertained. The assembly consists of a pan that is hung with a string thread, with the center of patch serving as an attachment point for the thread's other end. Weighing weights in a pan, the assembly will be handled like a beam balance. The weights needed to shatter the patch were applied.

pH measurement

pH meter was used for the determination of pH of the film-forming solution. The apparatus was calibrated with a buffer solution at pH 4, 7 and 10 prior of the experiment

Moisture content

Moisturecontentsof transdermal patches were determined by weighing each patch and keeping them in $CaCl_2$ desiccator for 24 hours. After a specific time, patches were weighed again, and differences in the weight were noted down.

%Moisture Content = Final Weight-Initial weight

Moisture uptake

Transdermal patches were placed in desiccators containing silica gel at RT for 24 hours, and then they were weighed (ws). The patches were then transferred to other desiccators and dried at 75% relative humidity using a saturated solution of NaCl at 250°C. The patches were repeatedly weighed until a uniform weight (wm) was achieved.

%Moisture Uptake = Final Constant Weight-Initial weight

Drug content

For determination of drug content, the known area of the patch was cut and dispersed in chloroform in a 100 mL volumetric flask. The flask was then kept in a shaking incubator for 4 hours. The solution obtained was filtered and 1-mL solution was taken. After diluting it in 10 mL chloroform, the absorbance of the prepared solution was measured at wavelength 267 nm under a UV-visible spectrophotometer.

In-vitro drug release studies

For the study of dissolution and release kinetics, a dissolution rate test apparatus (USP-II) was utilized. The film produced was applied to rat skin and secured to the diffusion cell with the drug-releasing side facing the receptor compartment, which contained a pH 7.4 phosphate buffer solution maintained at 37 ± 1°C. To ensure proper mixing, magnetic stirring was employed. At specified intervals, 5 ml samples were withdrawn and replaced with an equivalent volume of pH 7.4 phosphate buffer. The released drug was then analyzed using a UV spectrophotometer at 268 nm.[8,9]

Table 2: Parameters of evaluation of transdermal patches of apigenin

FC	*Thickness (mm)*	*Weight variation (mg)*	*Flatness*	*Folding endurance*	*Tensile strength (kg/mm2)*	*pH*
TP1	0.19 ± 0.03	± 1.98	100	240.2 ± 0.92	9.28 ± 0.28	5.9
TP2	0.19 ± 0.07	± 1.87	100	234.3 ± 0.11	10.16 ± 0.11	6.1
TP3	0.19 ± 0.12	± 2.14	100	244.8 ± 0.25	10.39 ± 0.06	6.0
TP4	0.21 ± 0.20	± 2.17	100	252.4 ± 0.21	11.18 ± 0.04	6.2
TP5	0.18 ± 0.04	± 1.16	100	258.9 ± 0.18	11.86 ± 0.03	6.3
TP6	0.19 ± 0.06	± 2.11	100	250.8 ± 0.26	11.02 ± 0.03	5.9
TP7	0.20 ± 0.09	± 2.13	100	249.2 ± 0.11	10.06 ± 0.12	6.0

Note: All reading of Mean ± SD; n = 3

RESULTS AND DISCUSSION

Apigenin drug was selected for the present study after thoroughly going through the literatures. After checking various compatibility parameters, Span 80, propylene glycol, ethyl cellulose and HMPC E5 are selected as excipients for the present study. Various ratios of polymers were used for the development of patches, as discussed in the ethods. Seven different patches were developed by using different ratios of polymers. The developed patches underwent various evaluation tests for their physical and chemical characteristics, such as pH, tensile strength, folding endurance, flatness, moisture uptake, moisture contents, drug contents, weight uniformity, thickness and appearances. The results of these evaluation parameters are mentioned in Table 2. The developed therapeutics were found to be free from any entrapment bubbles, flexible, uniform, smooth and clear. Both moisture uptake and moisture content were found to be increasing with increasing the concentration of polymers. Moisture content and moisture uptake were in the satisfactory range. The hydrophilicity of the polymer was found to be directly proportional to the moisture uptake and moisture content levels. Low moisture contents signify higher stability of the therapeutics, but some amount of moisture is necessary to prevent the therapeutic from getting completely dry. Low moisture uptake prevents microbial contaminations and reduces the bulkiness of the therapeutics.

The developed therapeutics were found to be free from any entrapment bubbles, flexible, uniform, smooth and clear. The thickness of the patches was determined using a digital thickness gauge.

The range of thickness of patches was found to be between 0.18 and 0.22. 10. Weight variations were also determined for the formulations. For the flatness of 5 randomly selected transdermal patches, a result obtained showed 100% flatness. Folding endurance was determined to understand the brittleness of the developed formulation and the stability and force it can withstand while being folded. Folding endurance for the developed therapeutics was found to be between 234.3 and 258.9 units. A tensile strength study was performed to determine the mechanical properties of transdermal patches. The tensile strength of the developed therapeutics was found to be in the range of 9.28 and 11.86 units. pH of the developed patched containing AN as API were found to be within satisfactory and acceptable range.

Moisture content and uptahe (table 3) of the developed patches were determined and results were given. Also drug content of TP-An was determined and of TP5, it was maximum, i.e., 98.67 ± 0.24% (Table 4).

Table 3: Moisture content & uptake of TP of apigenin

FC	*%Moisture content*	*%Moisture uptake*
TP1	2.19 ± 0.06	4.98 ± 0.11
TP2	2.36 ± 0.11	5.03 ± 0.28
TP3	2.48 ± 0.23	5.10 ± 0.06
TP4	2.54 ± 0.28	5.06 ± 0.41
TP5	1.88 ± 0.23	3.02 ± 0.22
TP6	1.93 ± 0.21	3.49 ± 0.17
TP7	2.13 ± 0.03	3.35 ± 0.09

Note: All reading of Mean ± SD; n = 3

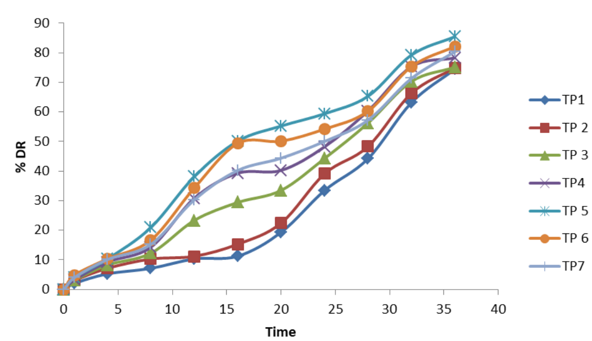

Figure 1: Cumulative %drug release of transdermal patches containing apigenin

Figure 2: Transdermal patches containing apigenin (AN); formulation code TP5

Table 4: DC of TP of apigenin (AN)

FC	*%Drug content*
TP1	96.20 ± 0.11
TP2	97.39 ± 0.18
TP3	98.06 ± 0.31
TP4	98.52 ± 0.19
TP5	98.67 ± 0.24
TP6	98.02 ± 0.02
TP7	97.26 ± 0.17

Note: All reading of Mean ± SD; n = 3

Table 5: *In-vitro* release of TP of apigenin

Time (h)	*Cumulative %drug release*						
	TP1	*TP 2*	*TP 3*	*TP4*	*TP 5*	*TP 6*	*TP7*
0	0	0	0	0	0	0	0
1	2.10	3.02	3.10	3.31	4.10	4.88	4.10
4	5.27	7.13	8.26	9.26	10.29	10.32	10.11
8	7.14	10.28	12.25	14.29	20.92	16.68	15.21
12	10.32	11.21	23.32	30.81	38.12	34.28	30.29
16	11.24	15.29	29.39	39.29	50.12	49.36	40.21
20	19.32	22.43	33.48	40.23	55.22	50.11	44.36
24	33.45	39.10	44.28	48.21	59.39	54.20	50.03
28	44.20	48.31	56.22	60.31	65.29	60.24	57.21
32	63.12	66.29	70.28	75.28	79.20	75.28	71.29
36	74.46	74.89	75.08	78.26	85.43	82.11	80.32

Dissolution studies provide important data useful for understanding the controlled release pattern of API from the therapeutics. Transdermal patches are intended to release the drug in order to maintain a therapeutic level of API in the plasma. Dissolution studies were performed by using PBS pH 7.4, containing 20% methanol as dissolution medium (modified disc assembly). 37^{o}C was maintained during the complete study. Table 5 and Figure 1 contain complete data obtained from the *in-vito* drug release studies. Figure 2 shows optimized transdermal patches of apigenin.

CONCLUSION

TP5 transdermal patches composition has maximum drug content and drug relapse, and this formulation code was considered as the best formulation of apigenin transdermal patches.

REFERENCES

1. Parivesh S, Sumeet D, Abhishek D. Design, evaluation, parameters and marketed products of transdermal patches: A review. Journal of Pharmaceutical Research. 2010 Feb;3(2):235-240.
2. Dhiman S, Singh TG, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(5):26-34.
3. Jain A, Chhajed M, Saluja MS, Dwivedi S, Patel B. Treatment of Diabetes with Indian Herbs and Herbal Medicines: A Review. International Journal of Pharmacy & Life Sciences. 2023;14(3):6-32
4. Sharma N, Sharma S, Kaushik R. Formulation and evaluation of lornoxicam transdermal patches using various permeation enhancers. International Journal of Drug Delivery Technology. 2019;9(4):597-607. DOI: 10.25258/ijddt.9.4.14
5. Verma P, Bairagi D, Somkuwar A, Mehra M, Chajjed M. Formulation and Evaluation of Transdermal Patch of Glibenclamide. International Journal of Pharmacy & Life Sciences. 2020;11(7):6724-6737.
6. Tiwari C, Choudhary M, Malik P, Jaiswal PK, Chauhan R. Transdermal Patch: A Novel Approach for Transdermal Drug Delivery. Journal of Drug Delivery and Therapeutics. 2022;12(6):179-188. https://doi.org/10.22270/jddt.v12i6.5779
7. Alwan LA, Al-Akkam E. Formulation and Evaluation of Transdermal Dissolved Microneedles Patches for Meloxicam. International Journal of Drug Delivery Technology. 2021;11:656-662. DOI: 10.25258/ijddt.11.3.2
8. Patel K, Patel K, Zaveri M. Development, Optimization and Evaluation of Herbal Patch Formulation for Acne Treatment. International Journal of Pharmaceutical Investigation. 2023 Jan 1;13(1):74-81. DOI: 10.5530/223097131792
9. Dwivedi S, Gupta S. Formulation and evaluation of herbal gel containing Sesbania grandiflora (L.) poir. Leaf extract. Acta Chimica and Pharmaceutica Indica. 2012;2(1):54-59.