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DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCH CONTAINING COLCHICINE

Suraj B. Meshram, G. N. Dhembre*, U. T. Jadhao, S. T. Thoke, S. A. Wathore and Rathod D. A.

Department of Pharmaceutics SV.P. College of Pharmacy, Hatta, Dist. Hingoli, Maharashtra.

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***Corresponding Author: G. N. Dhembre**
Department of Pharmaceutics SV.P. College of Pharmacy, Hatta, Dist. Hingoli, Maharashtra.

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ABSTRACT

The present research work was intended to prepare transdermal patch containing Colchicine as a model drug. Matrix type of colchicine containing transdermal patch was prepared by solvent casting method using three rate controlling polymers like HPMCK4M, ethyl cellulose and PVPK30. Fixed concentration (2%) of all three polymers was utilized for the preparation of patch. Compatibility studyof drug with the excipients was determined by I.R. Spectroscopy, Thickness of the patch was measured by using screw gauge. The thickness of prepared patch was found in the range of 0.310 to 0.315 mm. Batch F3 showed highest thickness of patch. The weight of the prepared transdermal patches for different formulations ranged between 52.14±1.20 to 55.70±1.98 mg. The percentage of drug content of formulation batch F1 to F7 varied between 94.04±1.23 to 97.26±0.31%.The folding endurance value for all batch formulations was found within range of 64 to 87. Patches formulated with ethyl cellulose (F2) showed the patch formulation F1, F2 and F3, formulated with HPMC, ethyl cellulose, and PVP K30, without addition of permeation enhancer in fixed concentration i.e. 2%, showed drug release of 72.16±0.33, 61.12±1.40 and 66.53±0.62% at the end of 24 hrs respectively. The developed optimized matrix type transdermal patch formulation was found to be stable during the stability study for the period of 3 month indicating good stability of the product.

KEYWORDS: Colchicine, HPMC, Transdermal Patch, folding endurance etc.

INTRODUCTION

Transdermal drug delivery systems (TDDS) represent a pivotal advancement in pharmaceuticaltechnology, offering a non-invasive and convenient means of administering therapeutic agentsthrough the skin for systemic distribution. Unlike conventional routes of drug administrationsuch as oral ingestion or injections, transdermal delivery by passes the gastrointestinal tract andavoids first-pass metabolism, potentially enhancing drug bioavailability and therapeutic

efficacy while minimizing systemic side effects. This innovative approach utilizes the skin'sunique properties as a barrier and a reservoir, allowing for controlled release of medicationsover extended periods, thus improving patient compliance and overall therapeutic outcomes.[1] Transdermal Drug Delivery System (TDDS) are defined as self-contained, discrete dosage which is also known as patches. A transdermal patch or a skin patch is a medicated adhesion with minimal inter and intra patient variation. The main objective of transdermal drug delivery system is to deliver drugs in to systemic circulation in to the skin through skin at predetermined rate with minimal inter and intra patient variation.4-6 That will improve bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency,reduced side effects and improved therapy due to maintenance of plasma levels up to the end ofthe dosing interval compared to a decline in plasma levels with conventional oral dosage forms.[2]

The development of transdermal delivery systems has revolutionized the treatment of various medical conditions ranging from chronic pain management to hormone replacement therapy. By harnessing the principles of diffusion, permeation, and drug partitioning across the skin layers.[3,4]

The skin acts as a formidable barrier to the penetration of drugs and other chemicals; it does have certain advantages which make it an alternative route for systemic delivery of drugs. Transdermal drug delivery system involves the passage of substances from the skin surface through the skin layers, into the systemic circulation. The skin has been commonly used as a site for topical administration of drugs, when the skin serves asa port for administration of systemically active drugs. The drug applied topically is distributed following absorption, first into the systemic circulation and then transported to the target tissue, which can be relatively remote from the site of drug application to achieve its therapeutic action.[5,6]

MATERIALS AND METHOD

Materials

Colchicine was received as a gift sample from Cipla Ltd, Mumbai, India. HPMC received from Colorcon asia pvt Ltd Goa. All other materials like PEP, TWEEN 80, PEG200, Piperine was of analytical grade and procured from commercial sources.

Method

Formulation of Colchicine Transdermal Patch

Matrix type of colchicine containing transdermal patch was prepared by solvent casting method using three rate controlling polymers like HPMCK4M, ethyl cellulose and PVPK 30. Fixed concentration (2%) of all three polymers were utilized for the preparation of patch. Firstly, required amount of polymer were weight accurately and dissolved in 10 ml of solvent mixture (Chloroform and water in 1:1) ratio under mechanical stirring at 60^{o} C, so as to form uniform polymeric solution. Drug colchicine was weighed accurately and was dissolved separately in a mixture of surfactant (Tween 80) and plasticizer PEG 200 (40 % of polymer weight), according to Table 1. The drug solution was then added to the polymeric solution. Triethanolamine was added dropwise to above mixture in order to achieved the required skinpH condition (6.5 to 7). Above formulation mixture was then further mixed under mechanical stirring at 400 rpm (Remi, India) at a lower temperature 50 ºC. In order to see the effect of natural permeation enhancer on permeation rate of drug, the colchicine in different concentration was subsequently added to the polymeric mixture in batch F4, F5, F6 and F7. Finally, patches were obtained by casting the solution in pre lubricated petri dish ($40cm^2$) and were allow to dry

by placing inverted funnel on it, so as to facilitated controlled drying for 24 hours at room temperature. The dry films were removed and cut in required size (2x2cm) and then wrapped in aluminium foil and kept in a dessicator until used.[7,8,9] The details for the formulation of Colchicine transdermal patch was shown in table 1.

Table 1: Composition of Colchicine Transdermal Patch.

Batch Code	F1	F	F3	F4	F5	F6	F7
Colchicine(mg)	25	2	25	25	25	25	25
HPMC K4 M	2	-	-	2	2	2	2
Ethyl Cellulose (%)	-	2	-	-	-	-	-
PVPK-30 (%)	-	-	2	-	-	-	-
Tween80(ml)	0.1	0.	0.1	0.1	0.1	0.1	0.1
PEG200 (%)	40	4	40	40	40	40	40
Piperine (%)	-	-	-	0.2	0.5	0.7	1
Triethanolamine	q.s	q.	q.s	q.s	q.s	q.s	q.s
Chloroform: Water	10	1	10	10	10	10	10

EXPERIMENTALWORK

Pre formulation Studies

Pre formulation research was therefore done on the drug sample in order to identify it and determine compatibility. Comprehensive pre formulation data enable rational decision-making regarding formulation design, excipient selection, and process optimization to ensure the development of safe, effective, and stable drug products.

UV Spectroscopy

A stock solution of Colchicine was prepared by using phosphate buffer pH 7.4. Then UV Spectrum was scanned in the range 200-400nm by using Shimadzu 1601.

Drug Excipients Compatibility Studies

Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (Shimadzu, Japan). The pellets were prepared at high compaction pressure by using KBr andthe ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug.

Evaluation of Transdermal Patches Thickness

Thickness of the patch was measured by using screw gauge. The reading of thickness wasdetermined at three different points and average thickness was determined.[10]

Weight Variation

10 patches from each formulation were weighed individually and the average weight was calculated. The individual weight should not deviate significantly from the average weight.[11]

Drug Content

A specified area 2x2cm of patch was dissolved in mixture of chloroform and methanol. It was closed and shaked vigorously for 24 hours in a shaker. The resulting solution was filtered and the amount of drug present in the filtrate was determined by using UV spectrophotometer at246 nm.[12]

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it either breaks or develops visible cracks on folding number of times manually, whichwas considered satisfactory to reveal good patch properties. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. The number of times the films could be folded at the same place without breaking gives the value of folding endurance.[13]

Surface pH

The patches were allowed to swell by keeping them in contact with 0.5ml of double distilled water for 1h in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 min.

Percentage Moisture Uptake

The patches were weighed accurately and placed in a desiccators where a humidity condition of 80-90 % RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respectto initial weight.[14]

Percentage Moisture Loss

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until the show a constant weight. The percent moisture content is calculated as the difference between final and initial weight with respect to final weight. The following formula was utilised to calculate the percentage moisture loss.

In *Vitro* Release Studies

The release studies were performed using Franz diffusion cell, generally comprise of two compartments, one containing the active donor compartment and the other containing receptorsolution (receptor compartment), separated by barrier i.e. membrane. The cell consisted ofsampling port and temperature maintaining jacket. The outlet and inlet was connected withlatex tube so the jacket had stagnant water inside and heat was provided by hotplate. The stainless steel pin was used to stir the receptor solution using magnetic stirrer. Adialysis cellulose membrane was used as artificial membrane and was placed on receptor compartment and both compartments held tight by clamps. Phosphate buffer pH 7.4 was used as receptormedium. The volume of diffusion cell was 10 ml and stirred with bent stainless steel pin. Thetemperature was maintained at 37 ± 1°C with the help of hot plate. The study was carried outfor 24 hours and at predetermined time interval 1 ml sample was withdrawn and the samevolume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions. The withdraw sample was analysed spectophotometrically at 246 nm.[15,16]

Stability Studies

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. One formulation was selected for stability studies on the basis of physiochemical characteristics, in vitro drug release of the formulations. The formulation was subjected to accelerated stability studies as per ICH (The International Conference

of Harmonization) guidelines. The most satisfactory formulation was sealed in an aluminium foil and stored at 40±2ºC, 75±5% RH for 6 months in stability chamber. Patches were periodically removed and evaluated.[17,18,19]

RESULTS AND DISCUSSION

Compatibility Studies (FT-IR)

Both the polymer and pure drug's infrared spectra are examined. It has been found in this investigation that there is no chemical interaction between the polymer and Colchicine.The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the two substances.

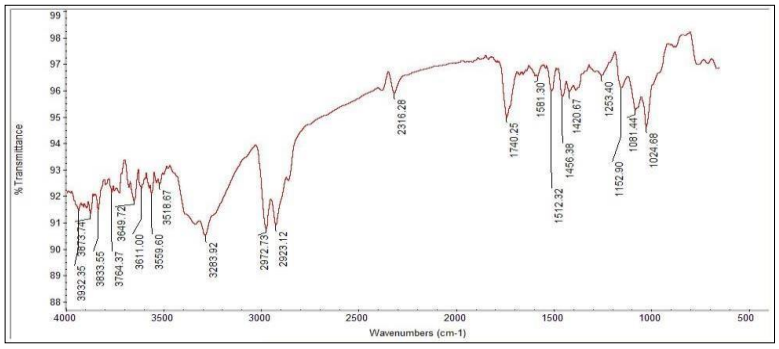

Figure 1: IR spectra of pure drug Colchicine.

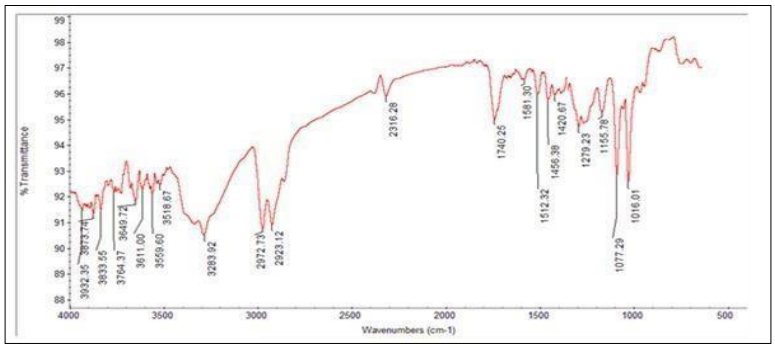

Figure 2: IR Spectra of Colchicine and HPMC K4M.

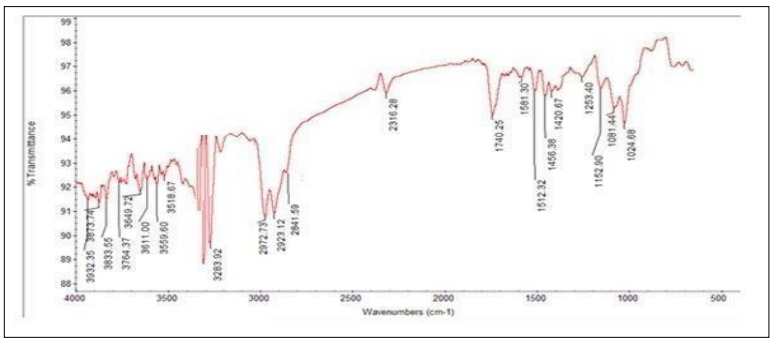

Figure 3: IR Spectra of Colchicine and Ethyl Cellulose.

Evaluation of Transdermal Patches Physical appearance

All the prepared patches were visually inspected for colour, clarity, entrapment of any air bubble, flexibility and smoothness. It was observed that all prepared patches had an characteristics colour and all patches formulation were free of bubble. All prepared patches shown smooth surface and enough flexibility.

Thickness

Thickness of the patch was measured by using screw gauge. The reading of thickness was determined at three different points and average thickness was determined. The thickness ofprepared patch was found in the range of 0.310 to 0.315 mm. Batch F3 showed highest thickness of patch. Low standard deviation values indicate low variation and uniformity in the formulation. The results were shown in table 2.

Weight Variation

10 patches from each formulation were weighed individually and the average weight was calculated. The weight of the prepared transdermal patches for different formulations ranged between 52.14±1.20 to 55.70±1.98 mg. The variation in weight uniformity of the prepared patches was found within acceptable range. The results were shown in table 2.

Drug Content

Drug content of the patch was carried out to ascertain that the drug is uniformly distributedinto the formulation. The percentage of drug content of formulation batch F1 to F7 varied between 94.04±1.23 to 97.26±0.31%. The percentage drug content for all batchformulations was within acceptable limit and indicated good drug containing capability. The results were shown in table 2.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at thesame place till it either breaks or develops visible cracks on folding number of timesmanually. The folding endurance of batch F1 to F7 was measured manually and data wereshown in the table 2 and figure 4.The folding endurance value for all batch formulationswas found within range of 64 to 87.Patches formulated with ethyl cellulose (F2)showed less folding endurance value, while those patches prepared with HPMC polymer, gives flexible patch as compared to ethyl cellulose and PVP K 30 and showed higherfolding endurance values. HPMC impart higher flexibility to patches. Among the formulation batch F7showed highest folding endurance. Overall all batch formulation gives satisfactory foldingendurance values. The results indicate that the patches would not break and wouldmaintain their integrity with general skin folding when used.

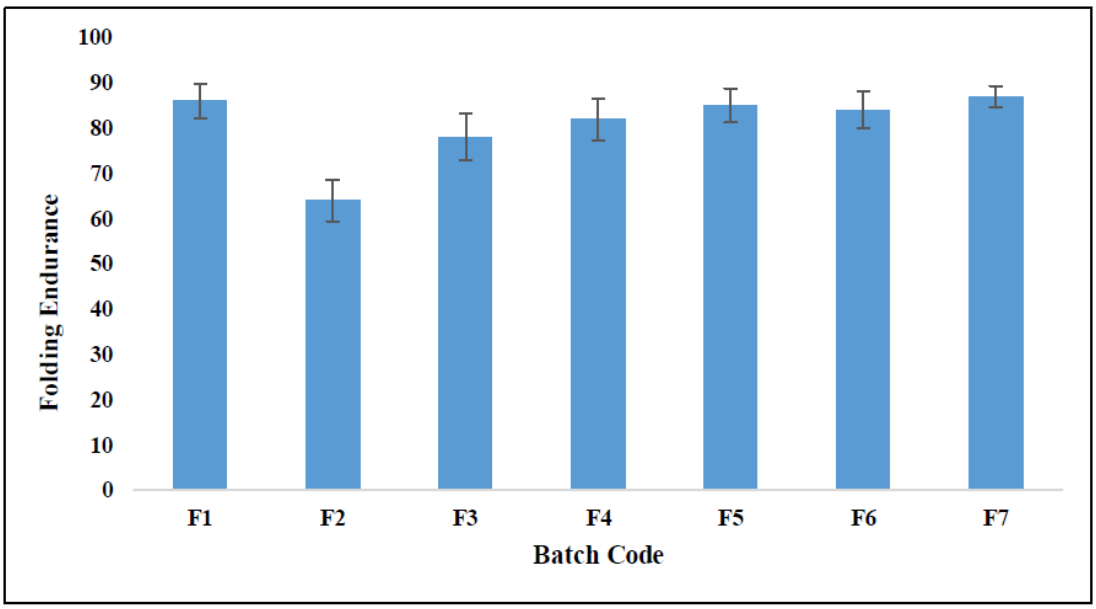

Figure 4: Folding endurance values of Batch formulation F1to F7.

Surface pH

The surface pH of all patches were determined and was found in the range of 6.6 to 6.8, ensuring compatibility of prepared patch formulation with skin. The results were shown in table 2.

Percentage Moisture Uptake

The percentage moisture uptake for all patch formulation was found in between 7.06±0.83to 8.32±0.72. Batch F3 showed highest moisture uptake, while F7showed minimum value, compare to others. All three hydrophilic polymers showed certain amount of moisture absorption. Moisture uptake for all batch formulation was in limit, which generally requiredbecause higher moisture uptake can be liable for microbial growth. The results of percentage moisture uptake value for all batch formulations was shown in table 2.

Percentage Moisture Loss

The Percentage Moisture Loss for prepared patch formulation was found to be between 2.06 ± 0.20 to 3.16 ± 0.22%. Patches prepared with PVPK30 (F3) showed highest percentage loss. The value of % moisture loss for all batch formulation was in limit, whichhelps to protect the patch to become brittle during storage.

Table 2: Evaluation of Colchicine Transdermal Patches (F1to F7).

Batch	Thickness (mm) ±SD*	Weight Variation (mg) ±SD*	Drug content (%)±SD*	Folding Endurance ±SD*	Surface pH (%)	% Moisture Uptake	% Moisture Loss
F1	0.310±0.021	52.14±1.20	95.23±1.06	86.16±3.78	6.6	7.10±0.64	2.10±0.21
F2	0.314±0.011	55.20±2.14	94.04±1.23	64.33±4.56	6.7	6.20±0.45	2.45±0.15
F3	0.315±0.014	54.62±1.61	96.31±1.36	78.15±5.19	6.6	8.32±0.72	3.16±0.22
F4	0.312±0.012	53.28±1.06	95.30±1.14	82.26±4.64	6.7	7.13±1.08	2.24±0.10
F5	0.314±0.018	54.42±1.38	96.14±0.66	85.10±3.80	6.6	7.22±0.40	2.45±0.14
F6	0.312±0.015	55.12±2.17	95.44±0.61	84.22±4.14	6.8	7.18±0.57	2.06±0.20
F7	0.312±0.008	55.70±1.98	97.26±0.31	87.31±2.27	6.8	7.06±0.83	2.18±0.17

*All values are mean ± SD (n=3)

***In Vitro* Drug Release Study**

The drug release from the prepared transdermal patch formulation was determined using Franz diffusion cell apparatus for the period of 24hrs. Phosphate buffer solution pH 7.4was use as diffusion medium. The results of colchicines drug release from patch formulation were showed in table 3.The graph was plotted between percentage drugrelease and time and it was showed in figure 5.

The patch formulation F1, F2 and F3, formulated with HPMC, ethyl cellulose, and PVP K30, without addition of permeation enhancer in fixed concentration i.e. 2%, showed drug release of 72.16 ± 0.33, 61.12 ± 1.40 and 66.53 ± 0.62% at the end of 24 hrs respectively. Patch prepared with ethyl cellulose (F2) show lowest amount of drug release as compared to HPMC and PVP K30, while patch prepared using HPMC (F1) showed optimum amount of drug release in 24 hr and hence selected further for the preparation of patch with natural permeation enhancer (Piperine). Patch formulation F4, F5, F6 and F7prepared with HPMC alone with varying concentration of piperine as permeation enhancer (0.25%, 0.5%, o.75% and 1% to polymer weight) showed drug release of 78.45±0.44, 82.51±0.94, 86.43±1.04and92.48±0.30%respectively. From the study it was observed that, drug release of colchicines was improved by addition of permeation enhancer piperine. As the concentration of piperine increases, the rate of drug release from the patch was also found to be increased. Drug release study clearly demonstrated that incorporation of

piperine as permeation enhancer significantly improved the drug release. Among the formulations, batch F7 formulated with HPMC(2%) along with piperine (1%)showed controlled drug release over a period of 24 hr when compare with other formulations and hence was selected as optimized formulation.

Table 3: *In-vitro* drug release study of Colchicine transdermal patch.

Time (hr)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	10.21±0.76	5.26±0.23	7.24±2.16	13.78±1.24	15.25±0.21	15.84±0.34	16.34±0.77
2	15.56±1.12	10.44±1.98	12.54±0.65	19.3±1.07	22.45±2.23	23.67±0.33	25.65±0.83
3	19.14±0.56	13.56±0.67	15.59±0.25	22.17±0.33	25.56±1.12	28.1±1.14	31.45±1.45
4	24.32±0.44	18.45±1.04	20.1±0.37	26.3±0.59	28.7±0.51	32.54±0.67	36.51±1.34
5	29.78±0.36	23.12±0.54	25.61±1.52	31.23±0.75	34.18±1.32	37.12±0.88	43.55±0.60
6	35.2±1.20	27.34±0.80	29.21±1.28	37.18±1.94	40.2±0.43	46.43±0.71	50.52±0.71
7	40.7±0.65	31.2±0.31	34.14±0.48	42.4±0.61	44.13±0.65	49.35±0.55	55.4±0.20
8	47.41±2.07	38.5±0.55	39.13±0.78	48.31±0.88	52.45±0.70	58.27±1.22	63.23±0.18
9	50.66±1.42	41.2±0.42	44.24±1.13	55.24±0.58	58.7±0.27	64.3±2.20	68.53±0.72
10	55.26±0.78	44.22±2.02	49.88±0.88	59.12±1.40	63.08±1.21	67.42±0.76	73.12±0.42
11	60.14±1.62	47.31±1.27	52.51±0.20	63.26±2.05	65.41±0.55	70.12±1.45	78.67±0.38
12	63.31±1.54	50.70±0.91	55.22±1.32	67.42±1.22	70.11±1.60	76.92±2.06	83.45±0.30
24	72.16±0.33	61.12±1.40	66.53±0.62	78.45±0.44	82.51±0.94	86.43±1.04	92.48±0.30

All values are mean ± SD (n=3)

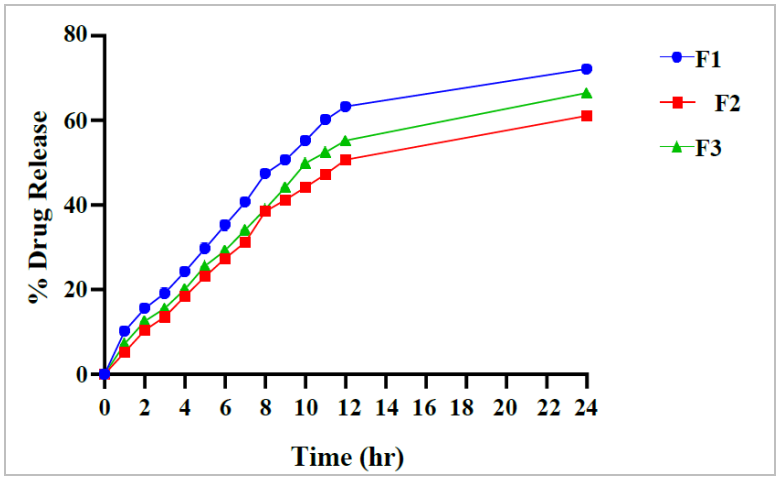

Figure 5: *In vitro* Release Profile of Formulations F1to F3.

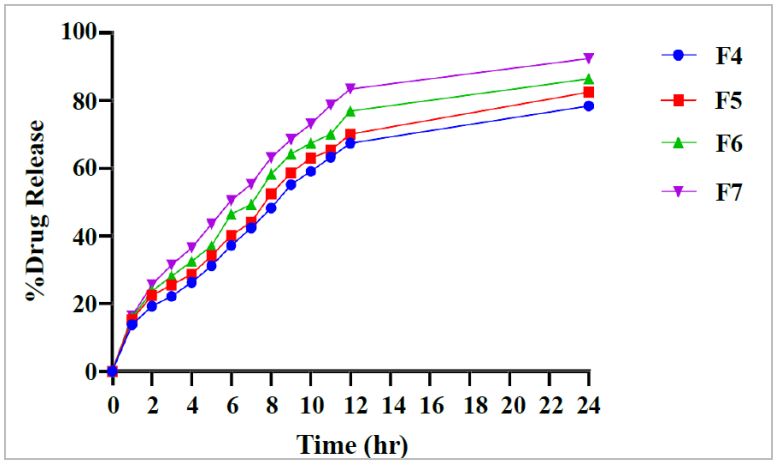

Figure 6: *In Vitro* Release Profile of Formulations F4 to F7.

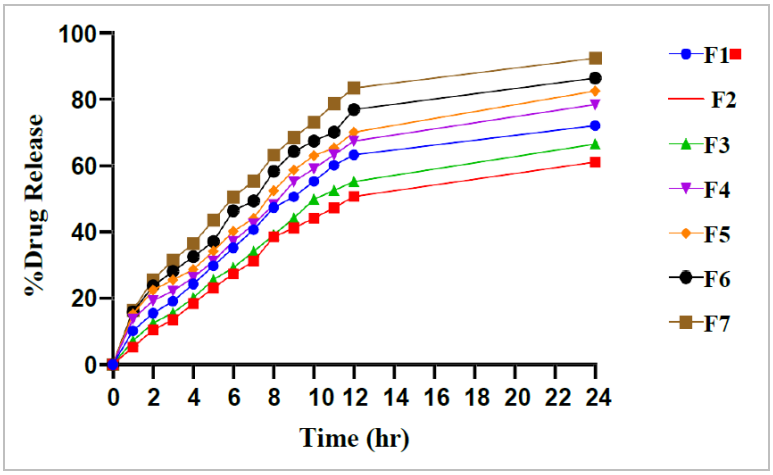

Figure 7: *in Vitro* Release Profile of FormulationsF1to F7.

CONCLUSION

The matrix type transdermal patches of colchicine can be effectively prepared by solvent casting method for the treatment of gout. HPMC K4M was found to be effective polymer in the development of transdermal patches of colchicine. All the prepared formulations were showed satisfactory results required for the transdermal patch type of products. IR- spectroscopic studies indicate no drug-excipient interaction in formulation. The in vitrorelease profile of all the prepared patches formulations were showed to extend the drug release over a longer duration. Piperine was found to be showed excellent natural drug permeation enhancing ability, when incorporated in transdermal patch formulation. Comparing the entire batch, F7was consider as the ideal formulation which on the basis of evaluation parameters. Future details investigation is required to establish *in vivo* efficiencyof colchicine contained transdermal patch and long term stability study need to be confirming the stability of colchicine transdermal patch.

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