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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF MEFENAMIC ACID

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ABSTRACT

The mefenamic acid patches were prepared by using HPMC K4M, Na CMC as a matrix film and using the PVP K90 was as a crystallization inhibitors. As a result, the characteristics showed the homogeneous patches without the crystal form of the mefenamic acid drug, indicating completely achieved crystallization inhibition of mefenamic acid drug in the drug- in- adhesive patches. The characterizations showed the homogeneous patches without the crystal form of the mefenamic acid in matrix patches. The release profiles of the mefenamic acid from the patches were investigated by Franz diffusion cells. Over the first 1 h, the release behavior of mefenamic acid from the patches obviously increased when PVP was used as a crystallization inhibitor. However, the ratio between drug: PVP K90 at 1:2 was found to be the most effective in increasing the drug release from patch. Thus, the PVP could be used as a crystallization inhibitor for mefenamic acid in matrix patches which will increase the drug release.

INTRODUCTION

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin [1].Treatment of chronic diseases such as asthma, rheumatoid arthritis by transdermal route of drug administration might prove to have several advantages over other routes of drug administration[2].The polymeric technologies have been honed and refined over the past several years and currently great interest has been focused on the development of novel drug delivery systems[3].

MATERIALS

Mefenamic acid (Gift sample from INTERMED PHARMA, Chennai), PVP K90 were obtained from sigma-Aldrich (USA), HPMC K4M (N R Chem,Bombay), Na CMC, Na benzoate,polyvinyl alcohol, propylene glycol, Na polyacrylate, Glycinal, All the polymers received were of pharmaceutical grade.Materials and solvent used were of chemical grade.

METHOD: (preparation of Drug in Adhesive patches)

Appropriate quantity of polyvinyl alcohol was soaked in water and mix to form clear solution. The amount of drug was dissolved in propylene glycol and Na benzoate. Solvent blend was transferred appropriate quantity of polyvinyl alcohol was soaked in water for continuous stirring [4,5]. The

polymer solution was dissolved in solvent and plasticizer, in to the solution was added gently to HPMC K4M, Na CMC, PVP K90 and mixed thoroughly with the help of magnetic stirrer for 30 minutes. The PVP K90 was the high potential act as a crystallization inhibitor. Then added Glycinal , Glycerine ,Na polyacrylate and stirrer for 5 minutes [6,7]. Mix the entire solution in the jacketed mixing vessel for 3.30 minutes under vaccum. The coating machine is loaded with non woven fabric and pp release liner and made ready for gel coating. Adjust the size of the non-woven and pp release liner as per the desired patch size of 10*14cm. The cutting roller in the end is cutting to form uniform patches. After drying at room temperature for 24 hours membrane kept in a desiccator until for physical characterization and in vitro evaluation.

EVALUATION AND CHARACTERIZATION:

Adhesiveness Test: Check the adhesiveness using initial adhesiveness test. A steel ball rolled on the sticky surface of inclinate plate. According to the position of the strength of the adhesive surface can stick to one of the biggest steel ball size, evaluate it initial adhesion. The ball number 18 (stick to the surface for not less than 5 sec)

Surface pH: Transfer one patch in a 250ml conical flask and add 70ml of water, sonicate it for 60 minutes with temperature at 40 degree celcius. Cool shake well to make it homogeneous and check the pH using calibrate pH meter (pH limit 4.5-8.0)

Pouch Integrity: Fill the desicator with water just below the level of the sieve, and add few drops of the methylene blue and mix to give a light blue colour. Take 1 patch and dip them into the water in the desicator and place the lid over the desicator. Connect the desicator to the vaccum pump switch `on' the vaccum pump. Apply 250ml of Hg pressure (-pressure) hold the vaccum for 2 minutes after the desired pressure in reached. Switch of the vaccum pump.Release the pressure slowly (at least 30 sec) and take out the pouch. Wipe them to dry with a clean dry tint for cloth defoil the pouch and absence of blue spots/moisture/water inside. If no blue spots/moisture or water infound inside the pouch,patches are passing the test.

Thickness of the patch: At five different positions the thickness of each patch was measured by using microscope dial gauge, screw gauge or micrometer and the average was calculated [8,9].

Weight Uniformity: The weights of five patches of 2cm radius were taken and the weight variation can be calculated [10].

Folding Endurance: The folding endurance of the prepared patch was measured manually. A strip of the film (4×3cm) was cut evenly and repeatedly folded at the same place till it was broken. The thinner the patch more flexible it is [11].

Percentage Moisture Content: The weight of the film was noted individually and kept in a desicator containing fuse calcium chloride at room temperature for 24hrs. After 24hrs, the film were again weighted and determined the percentage moisture content from the mentioned formula

%Moisture Content = Initial Weight /– Final Weight × 100

Moisture Uptake: The patches were placed in the desicators containing 200ml of saturated potassium chloride to get the humidity inside the desicators at 84%RH. After 3 days the films were taken and weighted, the percentage moisture absorption of the patch was found [12].

%Moisture absorbed = Final Weight – Initial Weight/ Initial Weight × 100

Drug Content: A specified area of patch was dissolved in a phosphate buffer (PH-3.4) solution and stirred. The content was transferred to a volumetric flask. The absorbances of the solution were measured at wavelength 254nm and determine the drug content [13,14].

FORMULATION OF TRANSDERMAL PATCHES:

	Mefenamic acid 500mg TRAIL-1 (F1)		Mefenamic acid 500mgTRAIL-2 (F2)		Mefenamic acid 250mg TRAIL-3 (F3)	
INGREDIENTS	**(mg per patch)**	**(for 1kg)**	**(mg per patch)**	**(for 1kg)**	**(mg per patch)**	**For 10 patches)**
Mefenamic acid	500mg	58.82gm	500mg	66.6gm	250mg	2.5gm
PG	360mg	42.35gm	450mg	60.0gm	450mg	4.5gm
PVP	30mg	3.5gm	30mg	4gm	45mg	0,45gm
Na benzoate	10mg	1.1gm	10mg	1.33gm	15mg	0.15gm
Glycerine	2800mg	329.4gm	2700gm	360gm	2875mg	28.75gm
Titanium dioxide	16mg	1.88gm	16mg	2.13gm	_	_
HPMC K4M	240mg	28.23gm	250mg	33.3gm	100mg	0.1gm
DM water	4081.6mg	480.18gm	3541gm	472.1gm	3.3gm	39gm
EDTA	4mg	0.47gm	3.oomg	0.4gm	_	_
Tartaric acid	38.4mg	4.51gm	_	_	_	_
Na polyacrylate	400mg	47.05gm	_	_	25mg	0.25gm
Glycinal	20mg	2.35gm	_	_	20mg	0.20gm
	8.5mg	**1kg**	**7.5gm**	**1kg**		

ANALYTICAL METHOD:

Standard Preparation: Weight accurately 32mg of mefenamic acid working standard into a 500ml volumetric flask, add 30ml of methanol, sonicate for 15 minutes. Cool and make up to the mark.

Sample Preparation: Put one patch in a Erlenmeyer flask with a ground glass stopped (Not necessary to remove the liner) add 50ml of methanol, warm in a water bath for 10 minutes and shake vigorously for 30 minutes. Further sonicate for 30 minutes and cool filter this solution through a poly tetra floro ethylene membarane filter (p.size 0.45micrometer) and reject first few ml of the filtrate. Repeate the same procedure on another patch and report the mean result of 2 hours.

Procedure: Inject 10 microliter of standard and sample from the sample and standard plate response, calculate the control of mefenamic acid in mg per patch. The drug content was calculated by using the equation obtained from the standard calibration curve. The experiment for each formulation was triplicated.

DRUG PERMEATION STUDY:

The in-vitro permeation study was carried out by using Franz Diffusion Cell and cellophane membrane. The Franz Diffusion Cell has receptor compartment of volume 50ml and internal diameter of 4.5cm. A transdermal patch was placed on one side of cellophane membrane. The medium on the receptor side was phosphate buffer PH 3.4. The temperature was maintained at 37±2°C. The receptor fluid was stirred by magnetic bead placed in the diffusion cell. During each sampling interval, samples were withdrawn and replaced by equal volume of fresh receptor fluid. The sample (1ml) was withdrawn at predetermined time interval and diluted with phosphate buffer PH 3.4 in 25ml volumetric flask. The sample was analyzed spectrophotometrically at 254nm [15].

***IN -VITRO* DRUG RELEASE:** The release profile of mefenamic acid from all matrix type transdermal patches was studied by USP dissolution apparatus V using 900ml of phosphate buffer PH 3.4 as a receptor compartment. The temperature of the water bath was set at 37±0.5°C with stirring constantly at 100rpm. At sampling time 0,1,2,3,4,5,6, and 8 hours, the receptor medium was withdrawn and then replaced with the equal volume of fresh receptor medium. The content of mefenamic acid in each sampling time was analysed by HPLC assay and compared to the calibration curve. The samples for each sample were evaluated in triplicate [16].

RESULT AND DISCUSSION

The spectrum of UV was analysed by UV/Visible spectroscopy and λmax was found to be 254nm at PH 3.4 as mentioned in table 2 (Figure 1) Endurance test result indicated that the patches would not break and would maintain their integrity with general skin folding when applied. However, percentage moisture content andpercentage moisture uptake studies indicated that increase in polymer concentration was inversely proportional to percentage moisture content and percentage moisture uptake (Table3) The cumulative release of mefenamic acid from the controlled release memparane was studied under USP dissolution apparatus using 900ml of phosphate buffer as a receptor medium [17]. The time for sample collection was 0, 1, 2, 3, 4, 5, 6, 7, and 8hrs. Each sample collection was analyzed by HPMC assay and compared to the calibration curve. The percentage of cumulative release of mefenamic acid 0%, 12.32±0.375, 20.42±0.046, 23.14±0.545, 26.12±0.288, 29.32±0.046, 32.54±0.254, 36.18±0.0288, 39.82±0.0265 respectively. The low permeability of drug and more side effect, transdermal drug delivery system of has been attempted. Transdermal films were evaluated for different physicochemical characteristic such as adhesiveness, surface pH, pouch integrity, thickness of patch and weight uniformity. The polymer (HPMC K4M, PVP K90, Na CMC) were studied by using PG (PEG400) as plasticizer, for easy penetration of drug, PVA and Glycerine has been selected. It is found that the crystals of mefenamic acid dispersed in the patches [18]. Study shows that as the concentration of polymer increase the adhesiveness, thickness of patch, weight uniformity and surface pH increase. PVP K90 is interesting to be used as a crystallization inhibitor for inhibiting the crystallization of mefenamic acid. The crystals of mefenamic acid are determined under a microscope after the solvent is evaporated . The mefenamic acid patches were cut into 1cm*1cm specimens from five different possition and then the thickness of each specimen was measured and weighted [19].

Each sample of mefenamic acid matrix patch was cut into 1cm*1cm squares, which were extracted in methanol by sonication method for 30 minutes. This F1 and F2 formula obviously increased the drug release compared to F3 formula. PVP K90 as a crystallization inhibitor due to high viscosity. It might be increasing the solubilization of the mefenamic acid in matrix transdermal patches [20].

Table 2: Preparation of Standard Curve of Mefenamic Acid

Concentration(mcg/ml)	Absorbance
2.5	0.045
5	0.0860
10	0.1635
15	0.2200
20	0.3210
25	0.4385
30	0.5645

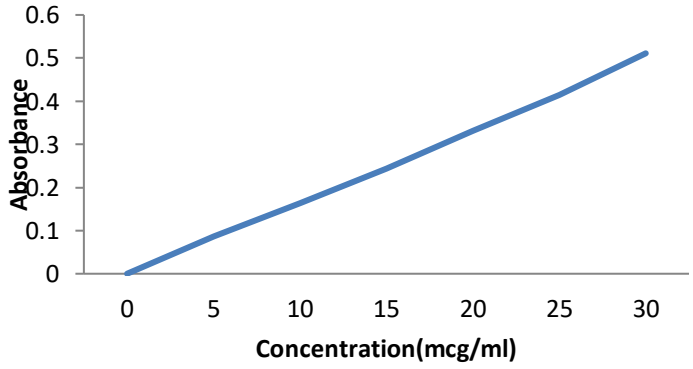

Figure 1: Standard Curve of Mefenamic Acid

Table 3: Evaluation of Mefenamic Acid Transdermal Patch

Formulation code	Thickness (mm)	Weight Uniformity (gm)	Folding Endurance	%Moisture Content	%Moisture Uptake	Surface pH	Drug Content (mg)
F1	0.76±0.05	0.512±0.01	132.0±2.5	5.26±0.11	4.80±0.32	4.68±0.12	70.65±0.45
F2	0.78±0.05	0.356±0.01	116.0±2.5	4.54±0.32	4.76±0.16	4.62±0.26	70.22±0.62
F3	0.82±0.06	0.404±0.00	100.0±2.0	4.43±0.54	4.73±0.48	4.90±0.02	69.43±0.40

Table 4: *In- vitro* drug release from F1, F2 and F3

Cumulative % drug release			
Time (hrs)	F1	F2	F3
0	0.00	0.00	0.00
1	6.32±0.062	8.43±0.547	12.32±0.375
2	14.22±0.142	16.33±0.407	20.42±0.046
3	16.45±0.230	18.56±0.356	23.14±0.545
4	18.24±0.345	20.35±0.045	26.12±0.288
5	20.46±0.046	22.57±0.089	29.32±0.046
6	22.42±0.091	24.53±0.298	32.54±0.254
7	25.16±0.544	27.27±0.065	36.18±0.0288
8	27.22±0.293	29.33±0.087	39.82±0.0265

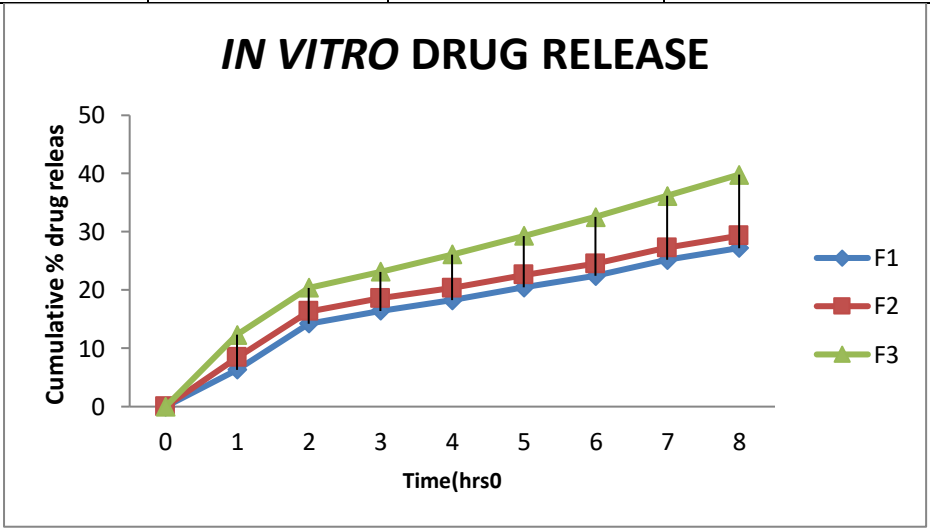

Figure 2: percentage of the cumulative release of mefenamic acid

CONCLUSION

The mefenamic acid patches were prepared by using HPMC K4M, Na CMC as a matrix film and using the PVP K90 was as a crystallization inhibitors. As a result, the characteristics showed the homogeneous patches without the crystal form of the mefenamic acid drug, indicating completely achieved crystallization inhibition of mefenamic acid drug in the drug- in- adhesive patches. The release amount of mefenamic acid from patches increased when PVP K90 was used as a crystallization inhibitor. PVP K90 was the high potential. In conclusion, the PVP act as a crystallization inhibitor for mefenamic acid drug- in- adhesivepatchesincreasing the drug release from the patches.

REFERENCES

1. Misra AN. Controlled and Novel Drug Delivery. In: N.K. Jain (Eds.), Transdermal Drug Delivery New Delhi, India: CBS Publisher and Distributor. 1997.100 -101.
2. Kulkarni VH, Keshavayya J, Shastry CS, Preeti VK. Transdermal Delivery of Antiasthmatic Drug through Modified Chitosan

Membrane. Indian J Pharm Sci. 2005;67:544– 7.
3. Siddaramaia PK, Divya KH, Mhemavathi BT, Manjula DS. Chitosan/HPMC Polymer Blends for Developing Transdermal Drug Delivery System. J Macro Sci Part A: Pure Appl Chem. 2006;43:601– 7.
4. Arul B, Sathyamurthy D. Formulation and evaluation of ketorolac tromethanmine gels. The Eastern Pharmacist 1998; 135-6.
5. Islam MT, Rodriguez-Hornedo N, Ciotti S, Ackermann C. Rheological characterization of topical carbomer gels neutralized to different Ph. Pharm Res 2004;21:1192-1199.
6. Chowdary KPR, Kumar PA. Formulation and evaluation of topical drug delivery systems of ciprofloxacin. Ind J Pharm Sci 1996; 58(2):47-50.
7. Tas C, Qzkan Y, Savaser S, Baykara T. In vitro release studies of chlorpheniramine maleate from gels prepared by different cellulose derivatives. IL Farmaco 2003; 58:605-11.
8. Patel RP, Patel G, Baria A. Formulation and evaluation of transdermal patch of Aceclofenac. International Journal of Drug Delivery 2009; 1:41-51.
9. Patel et. al. Formulation and evaluation of matrix type transdermal patches of Glibenclamide. International Journal of Pharmaceutical Sciences and Drug Research 2009; 1(1):46-50.
10. Kumar SS, Behury B, Kumar P. Formulation and evaluation transdermal patch of Stavudine. Journal of Pharmaceutical Sciences. 2013; 12(1):63-69.
11. Devi K, .Design and evaluation of matrix diffusion controlled transdermal patches of Verapamil Hydrochloride. Drug Dev Ind Pharm 2003; 5:495-503.
12. Mali AD, Bathe R, Patil M. An updated review on transdermal drug delivery system. International Journal of Advances in Scientific Research.2015; 1(06):244-254.
13. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal Drug Delivery System: A Review. The Pharma Innovation. 2012; 1(4):67-75.
14. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of Repaglinide. ISRN Pharmaceutics. 2011; 1-9.
15. Bangale GS, Rathinaraj BS, Rajesh KS, Shinde GV, Umalkar DG, Panicker PS. Design and evaluation of transdermal film of Atrnolol.J Chem Pharm Res, 2010;2(3):593-604.
16. Jain P, Banga AK. Inhibition of crystallization in drug – in-adhesive-type transdermal patches. International Journal of Pharmaceutics.1996;vol.394,no.1-2:68-74.
17. Suksaeree, Formulation development of matrix type transdermal patches containing Mefenamic acid: physicochemical characterization and in vitro release evaluation. Monatshefte fur Chemie-Chemical Monthly. 2017; Vol.148, no. 7, 1215-1222.
18. Suksaeree, Crystallization inhibition of Mefenamic acid for transdermal patches: Preliminary study. Thai J Pharm Sci. 2017; vol.41, 49-52.
19. Cesur S, Gokbel S. Crystallization of Mefenamic acid and polymorphs. Crystal Research and Technology. 2008; vol.43, no.7, 720-728.
20. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica. 2010; vol.67, no.3, 217-223.