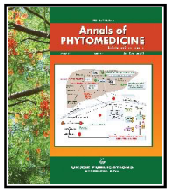
Annals of Phytomedicine 12(2): 972-979, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.2.116

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Formulation design and evaluation of aceclofenac transdermal patches

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Article Info

Article history

Received 11 November 2023

Revised 25 December 2023

Accepted 26 December 2023

Published Online 30 December 2023

Keywords

Penetration enhancer

In vitro diffusion studies

Transdermal patches

Compatibility

Release kinetics

Abstract

Transdermal drug delivery systems are a widely utilized method of drug delivery, and transdermal patches are used to treat a variety of disorders. They can help to avoid drug-related gastrointestinal issues and poor absorption. More and more research is being conducted on this subject, and with researchers growing interest in drug delivery; the number of transdermal devices entering the market is predicted to grow. Compatibility testing revealed no reaction between the drug and polymers. The drugs and polymers physicochemical compatibility, determined by differential scanning calorimetry and infrared spectroscopy, indicated the absence of any incompatibility. After one dose, the drug concentration rises to high levels throughout the system, at least immediately. The use of drugs to treat sickness has entered a period of tremendous expansion. Therapy with such formulations entails achieving and maintaining therapeutically effective drug concentrations in the body by introducing set dosages of a drug into the body at regular intervals. New polymers and penetration enhancers have been introduced, formulated by using HPMC, PVPK30 and by selecting solvents as chloroform and methanol plasticizer as dibutylphthalate penetration enhancers as propylene glycol and formulated F1 to F8 with various evaluation results such as folding endurance, drug content determination, tensile strength, thickness, and wt. variation. The highest-releasing formulation is found to be F4. The majority of researchers have been using HPMC as their preferred film-forming polymer.

1. Introduction

Transdermal route of drug delivery hence appears to be a good alternative approach to the oral route as it eliminates chances of drug loss by hepatic metabolism and provides healing patient compliance as opposed to other routes like the parentral route (Dunn and Legrand, 2004). Transdermal drug delivery offers an attractive alternative to oral administration and injection. Today about 74% of drugs are taken orally and are found not to be as effective as desired.

Drug delivery through the skin (for systemic effect) is commonly known as TDD and differs from traditional topical drug delivery, also known popularly as 'patches' (Pareek and Chandurkar, 2013). Transdermal patches are dosage forms designed to deliver a therapeutically effective amount of drug from the outside of the skin through its layers into the bloodstream.

Transdermal drug delivery systems (patches) are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin also defined as a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream (Pareek *et al*., 2011).

Macromolecules such as hormones, interferons and bioactive peptides can be divided by transdermal delivery system. Devices based on ethylene vinyl acetate copolymers. Devices based on silicone elastomer. This device is used as an implant. The matrix must have a channel to facilitate the release of macromolecules. Recent approaches iontophoresis built-in battery layer. Comparable in size to a normal transdermal patch (Dooley *et al*., 2011).

Asymmetric TPX membrane method was discovered by Berner and John (1994). In this prototype patch method can be prepared by using heat-sealable polyester film with a concave 1cm diameter as the backing membrane. Drug dispersed on the concave membrane, covered by a TPX (poly [4-methyl-1-pentene]) asymmetric membrane and sealed by an adhesive (Gonzalez -Alvaro *et al*., 2016).

Circular teflon mould method was discovered by Baker and Heller (1989). Polymeric solution in various portions is used as an organic solvent and the solution is divided into two parts. In one part, deliberate amount of the drug is dissolved and in another part, enhancers in different concentrations are dissolved and then two parts are mixed. Plasticizer (Di-N-butyl phthalate) is added into the drug polymer solution and the total contents are to be stirred for 12 h and then poured into a circular teflon mould. Moulds are to be placed on a level surface and covered with an inverted funnel to control solvent vaporization in a laminar flow with an air speed of 0.5 m/s solvent is allowed to evaporate for 24 h. After the dried film is formed, it is to be stored for another 24 h at 25 ± 0.5°C in a desiccators containing silica gel before evaluation to eliminate ageing effects (Brogden and Wiseman, 2019).

Mercury substrate method

They are prepared drug and plasticizer dissolved in polymeric solution. It is stirred for 10-15 min to produce homogenous dispersion, then it is poured into a level mercury surface and covered with an inverted funnel to control solvent evaporation (Dooley *et al*., 2011).

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By using the "IPM membranes" method, patches are prepared by dispersing water, polymer and drug. They are stirred for 12 h in a magnetic stirrer. Then dispersion is to be neutralized and made viscous by the addition of triethanolamine. Drug solubility in aqueous solution is very poor so solution gel is obtained by using buffer pH 7.4. Then formed gel will be incorporated into the IPM membrane (Ghosh and Barik, 2010).

By using the "EVAC membrane" method, carbopol reservoir gel polyethelene (PE) ethylene vinyl acetate copolymer (EVAC) membrane is demanded as rate control membrane. If, the drug is unable in water also use propylene glycol for gel medication (Sumedha Saxena *et al*., 2022). Drug is dissolved in propylene glycol, carbopol and resin will be added to the below solution and annulled by using 5% w/w sodium hydroxide solution. The drug (gel form) is placed on a distance of the backing subcaste covering the specified area. A rate-controlling membrane will be placed over the gel and the edges will be sealed by heat to gain a leak evidence device (Mehtab Ali *et al*., 2022).

Preparation of TDDS by using pro liposomes: By carrier system using film deposit fashion proliposomes are set. The drug and lecithin rate should be 0.1:2.0 taken as an optimized one from former references. For the medication of pro liposomes in a 100 ml round bottom beaker, take 5 mg of mannitol powder, also it is kept at 60-70°C temperature and the beaker is rotated at 80-90 rpm and dried the mannitol at a vacuum for 30 min. After drying, the temperature of the water bath is acclimated to 20-30°C. Drug and lecithin are dissolved in a suitable organic detergent admixture, a 0.5 ml aliquot of the organic result is introduced into the round bottomed beaker at 37°C, and after complete drying, alternate aliquots (0.5 ml) of the result is to be added. After the last loading, the beaker containing pro liposomes is connected to a lyophilizer and latterly drug loaded mannitol powders pro liposomes are placed in a desiccator overnight and also settled through 100 mesh. The collected powders are transferred into glass bottle and stored at the snap temperature until characterization (Tamanna Malik *et al.,* 2020).

By using the free film method, cellulose acetate film is prepared by casting it on a mercury face. And 2 w/w polymer results are prepared by using chloroform. Plasticizers are to be added at an attention of 40 w/w of polymer weight. Also, 5 ml of polymer result is poured in a glass ring which is placed over the mercury face in a glass petridish. The rate of evaporation of the detergent can be controlled by placing a reversed channel over the petridish. The film conformation is noted by observing the mercury face after complete evaporation of the detergent. The dry film will be separated and stored between the wastes of wax paper in a desiccator until use. Through this process, we can prepare free flicks of different consistency can be prepared by changing the volume of the polymer result (Brogden *et al*., 2016).

2. Materials and Methods

All the materials are procured from S.D Fine Chemicals Ltd, Mumbai, India. and Molychem, Mumbai, India.

2.1 Preparation method of calibration curve

2.1.1 Preparation of buffer solution

Dissolve 2.38 g disodium hydrogen orthophosphate 8.0 g sodium chloride and 0.19 g potassium dihydrogen phosphate in 1000 ml water. If required make adjustments to the pH 7.4.

2.1.2 Stock solution preparation

Stock A

To make drug stock media (1 mg/ml), dissolve 10 mg of the drug in 10 ml ethanol in a 10 ml volumetric flask (1000 gm/ml drug solutions) and shake vigorously and sonicated for about 10 min.

Stock B

To obtain a stock solution containing 100 g/ml of drug, 10 ml of this stock A is diluted to 100 ml with phosphate buffer pH 7.4. Whatman filter paper is used to filter the stock solution.

Final dilutions

The 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 and 1.2 ml samples are taken in each test tube, add phosphate buffer pH 7.4 to make a total volume of 10 ml to yield (2,4,6,8,10,12 µg/ml).

2.1.3 Calibration curve preparation

Phosphate buffer pH 7.4 was used to generate the standard solutions for the drug, which had concentrations of 2,4,6,8, and 10 µg/ml based on the stock solution. To obtain the linearity and regression equation, the absorbances of a pure drug solution containing aceclofenac were measured at 275 nm (λ max). A calibration curve was then produced between the drug concentration (µg/ml) on the x-axis and the absorbance on the y-axis.

2.2 Method of preparation of aceclofenac transdermal patches

Solvent casting is the procedure used for manufacturing aceclofenac transdermal patches. First, weigh the all ingredients as in the formulation table. Ingredients we used are drug, HPMC, PVPK30, chloroform, methanol, dibutylpthalate and propylene glycol. First, we weigh the HPMC, PVPK30 and add in chloroform methanol mixture and keep it aside for 2 h. After 2 h, add the drug, and stir it next, add the dibutyl phthalate little by little add to the solution and stir it. After that, add 1ml of propylene glycol and keep aside for 1 min. Take a petri dish, apply the glycerine, pour the solution into the petri dish and keep aside for 24 h. After that, remove the dried patch from the petridish (Table1).

3. Results

3.1 Determination of melting point

A substance melting point is the temperature at which it converts from a solid to a liquid condition. The melting point of pure crystalline solids is well characterized.

3.2 Solubility

Solubility is an important parameter for pre-formulation studies because it affects the dissolution of the medicine. Bioavailability of medicine is directly affected by oral administration and also by dissolution. The size of the particle, shape and surface region may affect the dissolution characteristics of medicine, hence it should be determined during pre formulation. Method counted volume of medicine was added to the suitable volume of detergent and the solubility checked (Table 3).

3.3 Calibration curve of aceclofenac

Calibration curve of aceclofenac is shown in Figure 1.

3.4 FTIR studies drug

Drug excipient studies are performed with FTIR spectroscopy in our college premises. Here are the peaks as shown below.

Table 1: Formulation transdermal aceclofenac patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Hydroxy propyl methyl cellulose (mg)	200	250	220	300	225	230	240	245
Dibutyl pthalate (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Poly vinyl pyrroliddone K 30 (mg)	250	200	230	150	225	220	210	205
Chloroform: Methanol	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Propylene glycol (ml)	1	1	1	1	1	1	1	1

Table 2: Determination of melting point

Trials	Melting point observed	Average melting point	Reference melting point
1)	149	150.3	149-153^0 C
2)	153		
3)	149		

Table 3: Solubility of aceclofenac pure drug

S. No.	Solvents used	Observation
1.	Phosphate buffer solution pH 7.4	Easily solubilized
2.	Ethanol	Easily solubilized

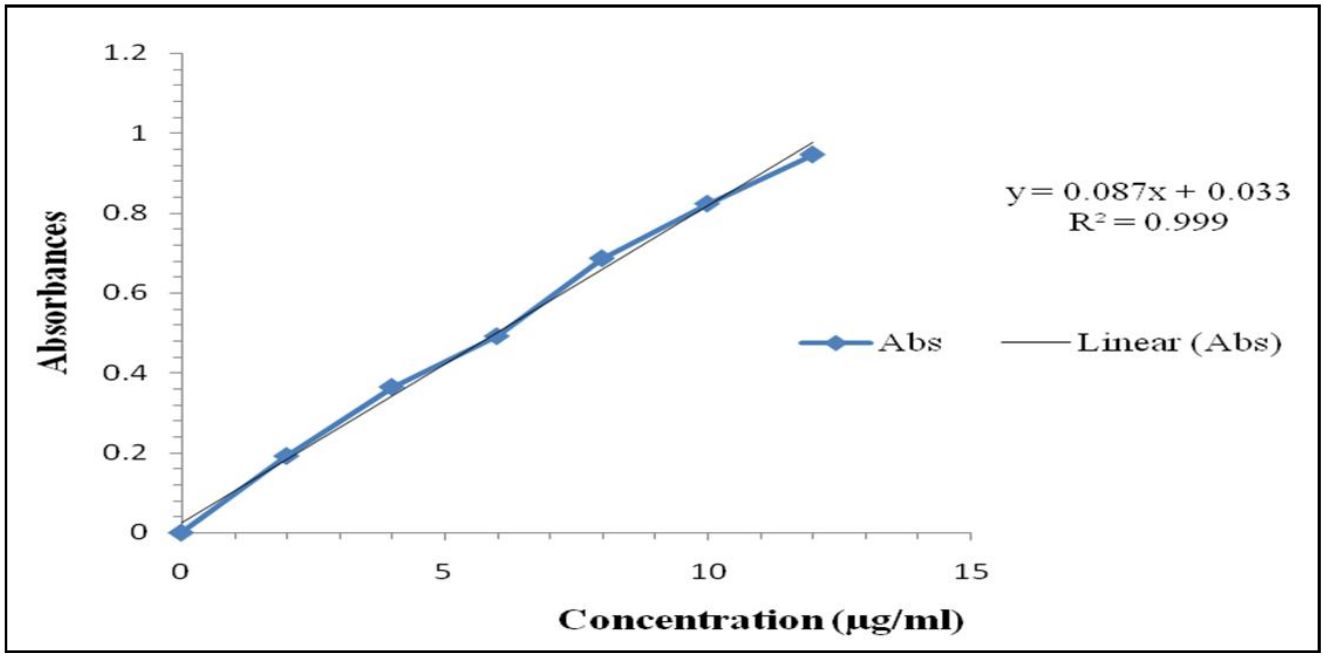

Figure 1: Standard curve of aceclofenac in phosphate buffer 7.4.

Table 4: Aceclofenac pure drug FTIR spectra show the following major bands at wave number

Functional groups	Wave numbers (cm^{-1})
N-H stretching	3319.24
Carbonyl stretching	1771.5 and 1716.7
Alkyl amine	1150
Aromatic C=H stretching	749

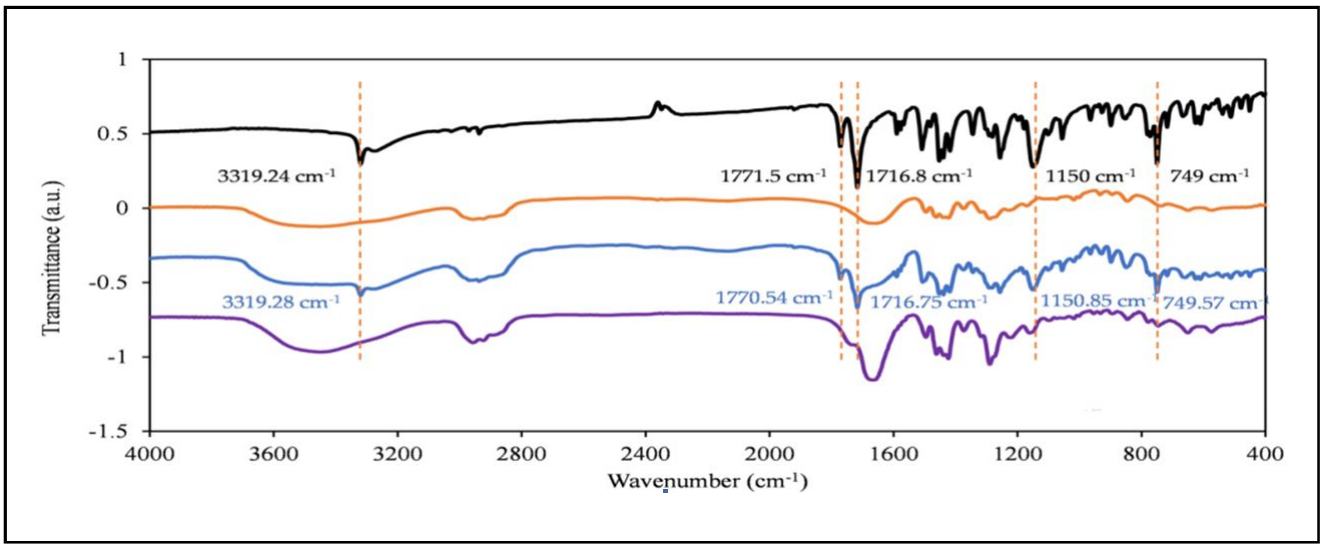

Figure 2: FTIR of aceclofenac (black), PVPK 30 (orange), a mixture (blue), and an aceclofenac containing formulation (purple).

3.5 Evaluation studies of aceclofenac transdermal patches

Table 5: Various evaluation tests for transdermal patches of aceclofenac

Formulation code	Thickness (µm)	Weight variation (mg)	Drug content (%)	Folding endurance	Tensile strength ($kgcm^{-2}$)
F1	162 ± 2.55	11.61 ± 0.17	90.9 ± 2.42	197 ± 66.12	2.86 ± 0.120
F2	165 ± 23.80	10.21 ± 0.31	91.6 ± 2.45	200 ± 6.57	2.25 ± 0.005
F3	163 ± 5.72	11.74 ± 0.34	90.5 ± 2.41	203 ± 6.54	2.58 ± 0.111
F4	167 ± 5.35	10.09 ± 0.43	96.9 ± 2.39	222 ± 6.51	2.98 ± 0.118
F5	165 ± 5.41	10.73 ± 0.37	91.8 ± 2.45	219 ± 6.57	2.54 ± 0.154
F6	160 ± 5.44	10.31 ± 0.31	90.5 ± 2.75	218 ± 7.63	2.45 ± 0.155
F7	161 ± 5.58	11.73 ± 0.46	91.5 ± 2.75	213 ± 6.87	2.87 ± 0.123
F8	163 ± 5.74	11.46 ± 0.46	90.5 ± 2.75	219 ± 6.54	2.35 ± 0.189

3.6 *In vitro* diffusion studies

Table 6: Formulation F1 to F8 *in vitro* diffusion studies

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	7.97 ± 0.22	6.45 ± 0.32	6.36 ± 0.11	8.53 ± 0.26	6.65 ± 0.29	5.65 ± 0.11	6.58 ± 0.55	5.32 ± 0.11
1	9.25 ± 0.24	10.58 ± 0.37	11.58 ± 0.25	13.78 ± 0.28	9.59 ± 0.57	10.59 ± 0.28	11.59 ± 0.54	12.59 ± 0.54
2	12.38 ± 0.14	13.89 ± 0.58	14.74 ± 0.19	18.95 ± 0.24	11.96 ± 0.14	15.96 ± 0.62	11.96 ± 0.15	16.96 ± 0.56
3	19.96 ± 0.58	20.89 ± 0.54	21.45 ± 0.17	26.71 ± 0.26	20.78 ± 0.66	22.78 ± 0.45	21.78 ± 0.28	22.78 ± 0.62
4	30.87 ± 0.54	31.58 ± 0.42	32.56 ± 0.15	40.78 ± 0.27	30.87 ± 0.64	31.87 ± 0.55	32.01 ± 0.27	35.87 ± 0.63
6	53.86 ±0.57	54.67 ± 0.47	55.45 ± 0.18	60.78 ± 0.35	53.64 ± 0.63	54.24 ± 0.22	54.89 ± 0.63	55.41 ± 0.64
8	70.55 ±0.22	71.32 ± 0.14	73.21 ± 0.25	79.43 ± 0.52	71.54 ± 0.67	70.29 ± 0.28	70.54 ± 0.27	70.57 ± 0.58
10	82.77 ±0.24	83.78 ± 0.19	84.52 ± 0.29	94.99 ± 0.68	82.98 ± 0.55	84.87 ± 0.45	85.52 ± 0.22	88.87 ± 0.55

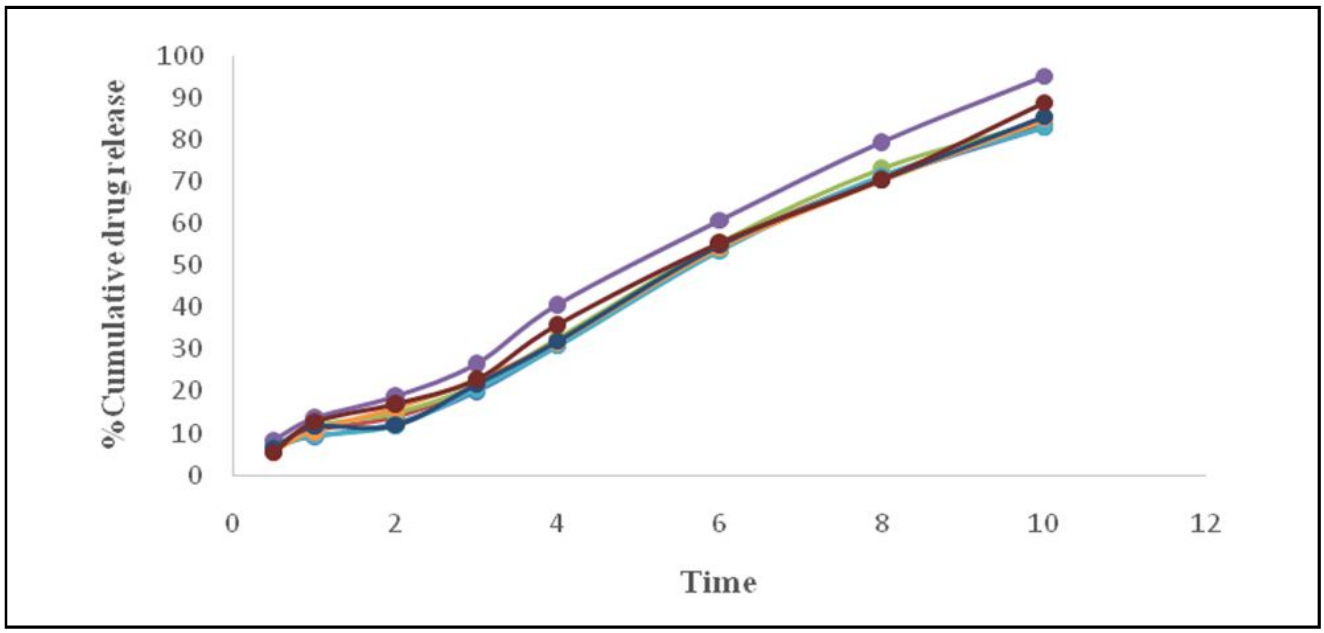

Figure 3: ***In vitro*** **diffusion studies of aceclofenac patches from F1 to F8.**

3.7 Surface morphology

Surface morphology of the tablet surface was conducted. It shows the magnification at X 500 size is 50 micrometers (Figure 4).

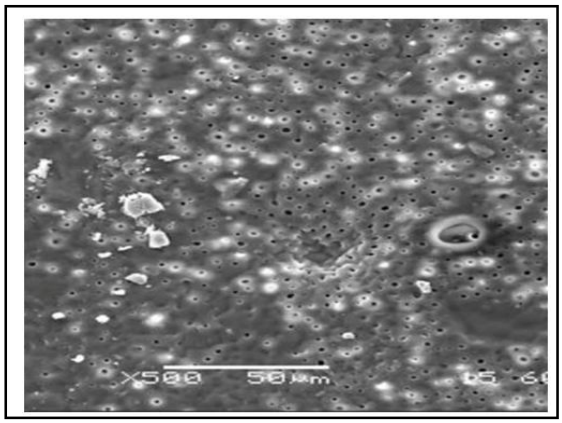

Figure 4: Surface morphology of tablet surface

3.8 Release kinetics studies

The plotting of the outcomes of *in vitro* release studies was done using several kinetic models. The values of the regression coefficient (R^2) for the Higuchi Model (0.894), Korsmeyer-peppas model (0.977), zero order (0.995) and first order (0.889).

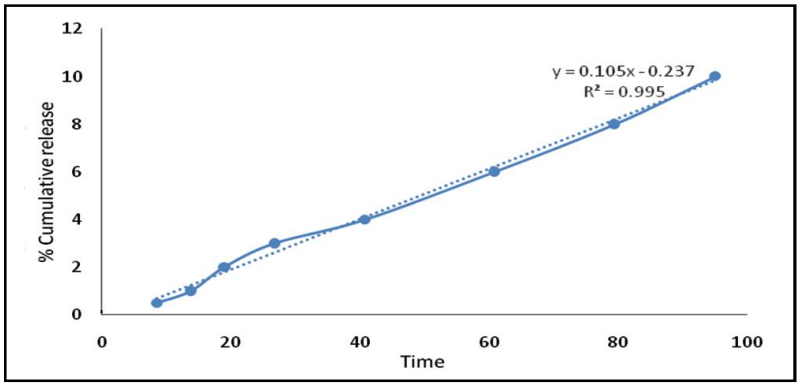

Figure 5: Zero order representation of optimized formulation.

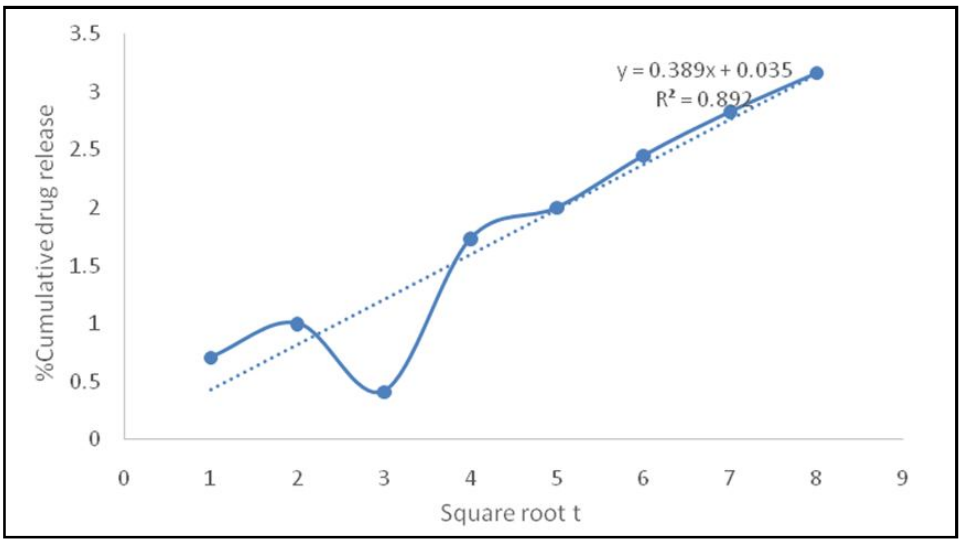

Figure 6: Higuchi plot representation of optimized formulation.

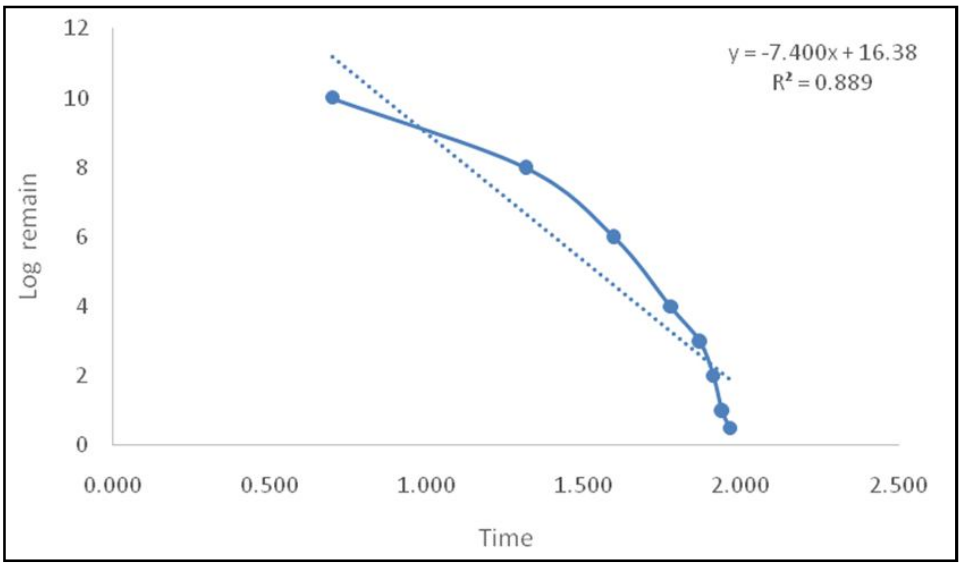

Figure 7: First order representation of optimized formulation.

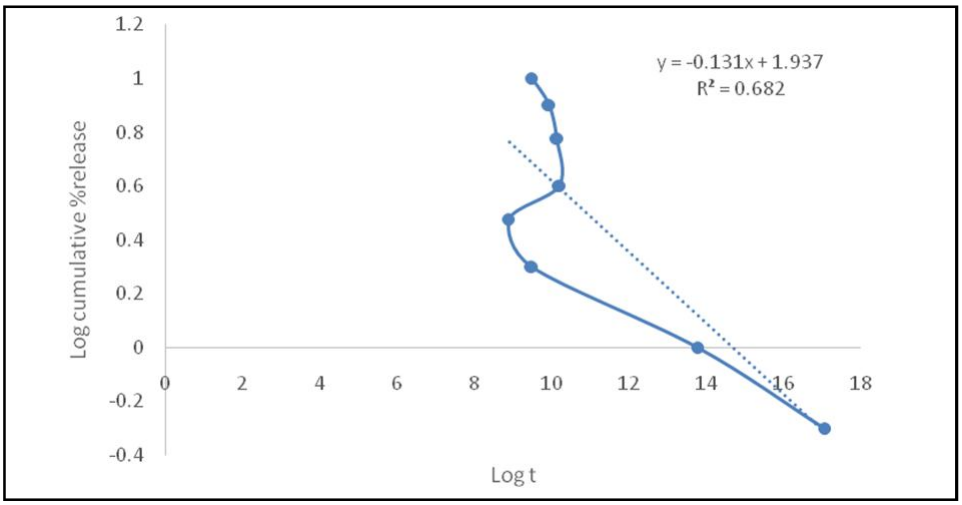

Figure 8: Peppas plot representation of optimized formulation.

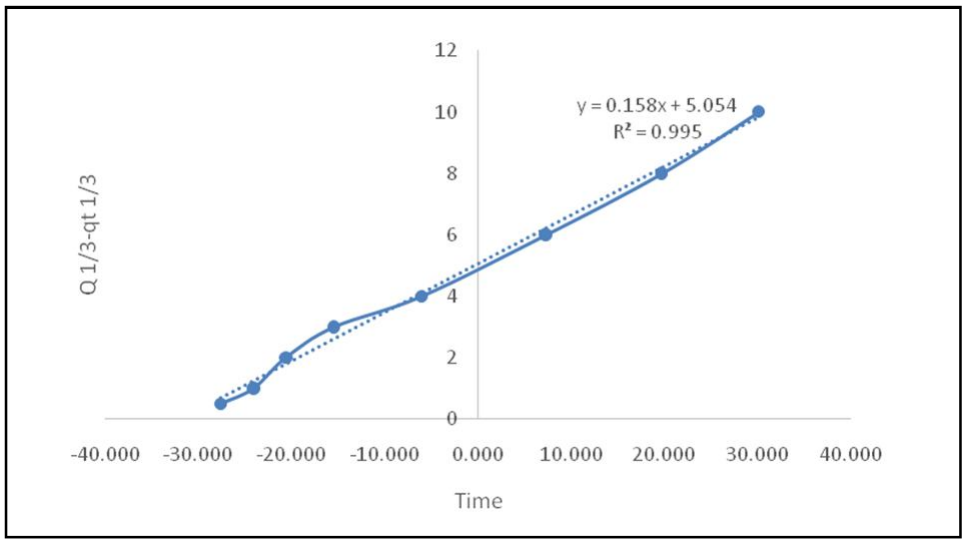

Figure 9: Hix cor plot representation of optimized formulation.

4. Discussion

4.1 Authentication studies

The capillary system is the official method for the determination of melting point. A narrow glass capillary tube containing a compact column of the drug to be determined is inserted into a heated stage (liquid bath or essence block) near a high delicacy thermometer in this system. The temperature in the heating step is ramped up at a fixed pace determined by the stoner until the drug in the tube converts to a liquid state (Table 2). Solubility is an important parameter for pre-formulation studies because it affects the dissolution of the medicine. Bioavailability of medicine is directly affected by oral administration and also by dissolution. The size of the particle, shape and surface region may affect the dissolution characteristics of medicine, hence it should be determined during pre-formulation. Method counted volume of medicine was added to the suitable volume of detergent and solubility checked. The calibration curve of aceclofenac is shown in (Table 4 and Figure 1). It shows the purity of the drug as per the graphs and data given. Drug excipient studies are performed with FTIR spectroscopy in our college premises. Here are the peaks as shown above. FTIR spectra peaks of the pure drug (aceclofenac), polymer (PVP), physical mixture and formulation are done. The peaks found overlay after mapping in IR spectra are N-H stretching (3319.24), carbonyl stretching (1771.5 and 1716.7), alkyl amine (1150) and aromatic C=H stretching (749). By this peak, we can confirm the drug excipient and physical mixture and formulation are inert with each other (Table 5 and Figure 2).

4.2 Evaluation studies of aceclofenac transdermal patches

Evaluation of formulated aceclofenac transdermal patches from F1 to F8 is done in three times. The evaluation tests conducted for patches are weight variation, thickness, tensile strength, drug content determination and folding endurance. The thickness of transdermal patches ranges from 160 ± 5.44 to 167 ± 5.35. The weight variation of transdermal patches falls from 10.09 ± 0.43 to 11.74 ± 0.34 The drug content of formulated patches is found to be 90.5 ± 2.41 to 91.8 ± 2.45. The folding endurance of the patch ranges from 197 ± 66.12 to 222 ± 6.51. The tensile strength of all the formulations is performed and they are in the range of 2.25 ± 0.005 MPa to 2.98 ± 0.118 MPa (Table 6.) *In vitro* diffusion studies of aceclofenac transdermal patches from F1 to F8 are performed by using Franz diffusion cell glass apparatus. The Franz diffusion cell is an apparatus that consists of a donor chamber and a receptor chamber that are separated by a water jacket. The egg membrane on which the formed patch is deposited separates the donor and receptor compartments. The phosphate buffer pH 7.4 is placed in the receptor compartment. Buffer is placed in the donor chamber. Temperature and RPM are kept constant. The data produced is of diffusion studies of aceclofenac transdermal patches from F1 to F8. The results are as follows. The studies were conducted for 10 h. F1 results were found to be from 7.97 to 82.77. F2 formulation results from 6.45 % to 83.78 %. F4 formulation results fall as 8.53 % to 94.99 % which is the highest drug release of all (Table 7 and Figure 3). Surface morphology of the tablet surface was conducted. It shows the magnification at X 500 size is 50 micrometers (Figure 9). The plotting of the outcomes of *in vitro* release studies was done using several kinetic models. The values of the regression coefficient (R^2) for the Higuchi model (0.894), Korsmeyer-peppas model (0.977), zero order (0.995), and first order (0.889). This showed that since the zero order kinetic model's R^2 value is higher, it is the model that best fits the release data. Model fitting discovered that aceclofenac transdermal patches displayed inconsistent transport (Non-fickian) mechanism for the drug release based on the "n" value (0.009 which is > 0.8) whereas R^2 was found to be 0.989 (Figures 4, 5, 6, 7 and 8).

5. Conclusion

Aceclofenac transdermal patches are manufactured by adopting solvent casting method using aceclofenac, PVPK30, dibutyl phthalate, HPMC, propylene glycol, chloroform, and methanol. Patches are cut to the size of 2 cm to 2 cm. Evaluation of transdermal patches is performed as per standards. The evaluation tests performed are thickness, weight variation, tensile strength, folding endurance, drug content determination, *in vitro* diffusion studies, and release kinetics studies. The results are produced for F1 to F8. The difference in the results is because of excipients like dibutyl phthalate and hydroxyl propyl methyl cellulose. Solvents help in swelling the polymer on optimum level. Release kinetics of optimized formulation has been

done and it falls in zero order and the Hixson crowell model. Transdermal patches deliver medicines directly into circulatory system, by passing through gastrointestinal system and avoiding the hepatic first pass effect. Aceclofenac transdermal patches are manufactured utilizing the solvent casting technique with, HPMC, PVPK30, solvents chloroform, methanol, plasticizer as dibutyl phthalate, penetration enhancer as propylene glycol. Formulation F4 shows the best results in all the evaluation tests in diffusion studies 94.99%. The thickness was 167 ± 5.35, weight variation was 10.09 ± 0.43, folding endurance was 222 ± 6.51, drug content was 96.9 ± 2.39, tensile strength was 2.98 ± 0.11. It concludes that all the above results of F4 are good compared to other formulations. The release profile of medicine through patches amplified when the attention of hydrophilic polymer was improved. Colorful phrasings were developed using hydrophilic and hydrophobic polymers such as HPMC and PVPK30 independently.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Ch. Shanthi Priya, Kotha Mounika, Nimmagadda Srinivas, Haarika Balusu and S. Rohini Reddy (2023). Formulation design and evaluation of aceclofenac transdermal patches. Ann. Phytomed., 12(2):972-979. http://dx.doi.org/10.54085/ap.2023.12.2.116.**