Vaibhav Farkiya *et al*, International Journal of Pharmaceutical Sciences & Medicine (IJPSM), Vol.7 Issue. 5, May- 2022, pg. 60-71

ISSN: 2519-9889
Impact Factor: 5.721

Formulation and Evaluation of Transdermal Patch of Chloroquine Phosphate

Vaibhav Farkiya; Sunita Patidar; Rajat Pawar
Swami Vivekanand College of Pharmacy, Indore
DOI: 10.47760/ijpsm.2022.v07i05.006

ABSTRACT: The aim of the present study was to investigate the patch for transdermal chloroquine delivery in an effort to mask the bitter taste when orally administered. Chloroquine has easily measurable outputs that are linked to increased renal Na^+ excretion. We thus monitored urinary Na^+ output in separate groups intravenously administered chloroquine or topically applied patch. Transdermal therapeutic systems are high- tech patches that make treatment much more convenient and pleasant for patient .Instead of having to take lots of tablets, patients often only have to apply a new patch once a week In addition, patches from LTS also ensure a constant drug level for the entire duration of wear Symptoms upon getting up in the morning as a result of low drug levels during the night are avoided. There are five major advantages of transdermal patches above other systems like Improved well –being for patient, constant drug levels, fewer side effects, Drugs that cannot be absorbed via the gastrointestinal tract can now be used and because the substance is released evenly and directly into the blood stream, less of the substance may be required**.**
Keywords: Transdermal patch, chloroquine phosphate, Malaria, topically

1. INTRODUCTION

1.1 Malaria:

Malaria is a vector-borne disease caused by a protozoan parasite of the genus *Plasmodium* and transmitted by the bite of an Anopheles mosquito. Four species of malaria parasite infect humans, namely*: Plasmodium vivax, Plasmodium malariae, Plasmodium ovale and Plasmodium falciparum. P. falciparum* causes the majority of infections in Africa and is responsible for most severe disease, large proportion of morbidity and mortality. *P. vivax and P. ovale* form the resting stages in the liver (hypnozoites) that once reactivated can cause a clinical relapse many months after the initial event [1] *Other species plasmodium* exhibit a similar life cycle with only minor variations. For instance a proportion of a form of parasites, hipnozoites from P. *vivax and P. ovale* remains dormant in the liver cells before undergoing asexual replication. Relapse can occur any time after the primary attack due to re-activation of a hypnozoites. Whereas relapse usually occurs within the first two or three months of the

ISSN: 2519-9889
Impact Factor: 5.721

primary attack malaria due to re-activation of a hypnozoites, there are reports that P. *vivax* hypnozoites can produce clinical infection 1–3 years after the original attack [1]

1.2 Transdermal drug delivery system

The most common and popular route of drug delivery is the oral route. However, this route of administration suffers from some significant drawbacks including first pass metabolism and drug degradation in gastrointestinal tract due to enzymes, pH etc. The idea of delivering drugs through skin is old, as the use is reported in 16th century in which the husk of castor oil plant in water was placed on an aching head [4] transdermal drug delivery system (TDDS), transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver drug through the skin and to the systemic circulation at a predetermined rate over a prolonged period of time[5] Transdermal patches offer added advantages such as maintenance of constant and prolonged drug level, reduced frequency of dosing, minimization of inter- and intra-patient variability, self-administration, and easy termination of medication, leading to patient compliance[6]

Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. For effective Transdermal drug delivery system, the drugs are easily able to penetrate the skin and easily reach the target.[7]

2. MATERIALS AND METHOD: Chloroquine Phosphate was received from Yarrow chem products Pvt. Ltd, Mumbai; Gelatin, PVP, Dibutyl Pthalate were analytical grade chemical and reagents procured and used.

3. PREFORMULATION:

3.1 Melting point determination:

Melting point of chloroquine phosphate was determined using capillary method. In this method little amount of chloroquine phosphate was filled in capillary after that the capillary was tied to a thermometer with the help of a rubber band. The thermometer with capillary was placed into Theil's tube which was previously filled with paraffin oil. The paraffin oil in the tube was heated until the drug melts. The temperature at which drug begins to melt was recorded.[24]

3.2 Determination of wavelength using UV spectrophotometric analysis:

50mg of chloroquine phosphate was weighed and dissolved into 50ml of water to prepare a 1000µg/ml stock solution from which a 10µg/ml dilution was prepared. Baseline correction was performed using water and sample was run between 200-400nm wavelength ranges in spectrum mode.[24]

ISSN: 2519-9889
Impact Factor: 5.721

3.3 Preparation of calibration curves:

The calibration curve of chloroquine phosphate were prepared in distilled water, 7.4 pH phosphate buffer and 6.8 pH phosphate buffer by using Shimadzu 1800 UV visible spectrophotometer.

Accurately weighed 50mg of chloroquine phosphate was transferred into a 50ml volumetric flask and the volume was made up with water to obtain a 1000µg/ml stock solution of chloroquine phosphate. From the stock solution 1ml was taken and transferred into a 10ml volumetric flask and rest of the volume was made up with water to obtain a 100µg/ml of solution from which 1 to 10µg/ml dilutions were prepared. Same procedure was followed for distilled water, phosphate buffer 6.8, and phosphate buffer 7.4 to prepare calibration curve respectively.[24]

3.4 Determination of Partition coefficient:

The Partition coefficient of chloroquine phosphate was determined by taking 20ml of octanol in a separating funnel and saturating it with 20ml of phosphate buffer pH 7.4 for overnight by intermittent shaking for 4h, keeping the separating funnel undisturbed for 1h after that 10mg of chloroquine phosphate was added into the separating funnel with moderate shaking for 24h. The two layers were separated and filtered through syringe filter and drug concentration was determined in both phases by UV-visible spectrophotometric method at 220 nm.[24]

3.5 Determination of solubility of chloroquine phosphate in various medium:

The solubility of chloroquine phosphate in various medium was determined by shake flask method. In this method 2ml of each solvent was taken into a vial and an excess amount of chloroquine phosphate was added. The vials were sealed properly and stirred for 10min. They were then kept on orbital flask shaker at 37°C for 24h. After solubilization of chlorouine phoqsphate, an extra amount of chloroquine phosphate was added to the vials containing drug-solvent mixture. The process was repeated until saturation solubility of chloroquine phosphate, indicated by presence of undissolved drug. The mixtures were then kept at room temperature for 24 h. and centrifuged using Remi 12C micro-centrifuge at 3000RPM for 15min. The supernatant were separated and diluted with respective solvents. The drug concentration was analyzed spectrophotometrically at 220nm using UV-visible spectrophotometer (Shimadzu-1800).[24]

3.6 Drug-excipient interaction study:

The compatibility of the drug was assessed by drug-excipient interaction study. The drug was mixed with various excipients in a 1:1 ratio in glass vials which were properly sealed and kept undisturbed at 40°C temperature for 14 days. After 14 days incompatibility was confirmed by TLC.[25]

ISSN: 2519-9889
Impact Factor: 5.721

3.7 Method of Preparing Transdermal Patches:

Method of preparation of TDDS was summarized by modifying the earlier reported methods. The patches were prepared by solvent casting method. The polymer (for example PVP/HPMC) was taken in a beaker with a minimum quantity of the solvent. Then 2/3rd of the solvent was mixed with the other polymers (for example PVA) and was added firstly with stirring at lower rpm and later at a higher speed. The plasticizer was added and homogeneously mixed and the drug was included with enduring agitation and the volume was made up. The films were cast onto a suitably designed and fabricated glass mould and then dried in oven at 40 °C. The films were removed by using sharp blade by inserting along the edges of the film. The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place. [26]

3.8 EVALUATION OF FORMULATION

- **Thickness of the patch:**

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.[27]

- **Uniformity of weight**

Weights variation is studied by individually weighting randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight[27]

- **Folding endurance:**

The patches were repeatedly folded at the same place till it broke. The number of times the patches could be folded at the same place without breaking gives the accurate value of folding endurance [27]

- **Percentage Moisture content:**

The prepared films are to be weighed individually and to be kept in a desiccator Containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula. Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.[28]

- **Percentage Moisture uptake:**

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula. Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100.[28]

ISSN: 2519-9889
Impact Factor: 5.721

- **Drug content:**

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.[28]

- ***In vitro* skin permeation studies:**

An *in vitro* permeation study can be using diffusion carried out by cell. Full thickness abdominal skin of male Wistar rats weighing of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals; an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectro photometrically.[29]

4. RESULT AND DISCUSSION:

4.1 Preformulation:

4.1.1 Melting point determination:

The melting point of was found to be **Chloroquine phosphate** 200 ˚C which is same as reported in literature**.**

4.1.2 Determination of wavelength using UV spectrophotometric analysis:

The maximum wavelength of was found **Chloroquine phosphate** to be 220 nm which matches the reported wavelength.

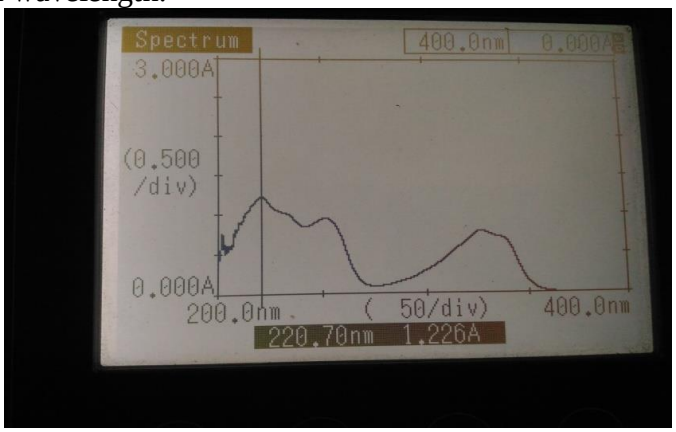

Figure-1: UV spectrum of Chloroquine phosphate

ISSN: 2519-9889
Impact Factor: 5.721

4.1.3 Preparation of calibration curves:

The calibration curves of chloroquine phosphate in various solvents e.g. distilled water, 6.8 pH phosphate buffer, 7.4 pH phosphate buffers were prepared and shown below:

Table No. 1: Absorbance data of chloroquine phosphate in distilled water for preparation of calibration curve, at 220 nm

S.No	Concentration µg/ml	Absorbance
01	05	0.203
02	10	0.412
03	15	0.612
04	20	0.812
05	25	0.974

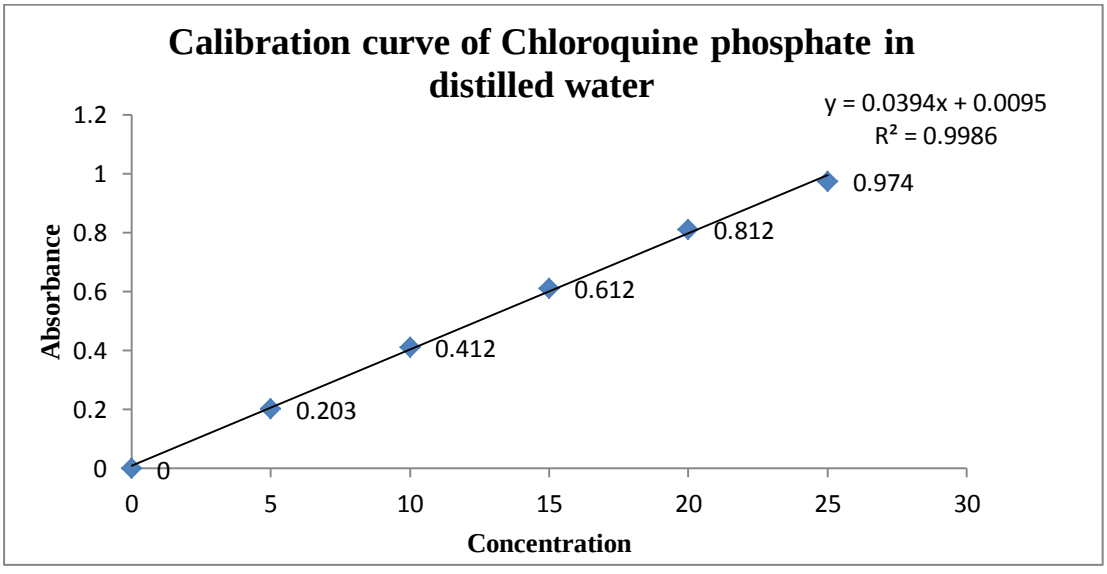

Figure-.2 Calibration curve of Chloroquine phosphate in distilled water

Table No. 2: Absorbance data of chloroquine phosphate in phosphate buffer pH 6.8 for preparation of calibration curve, at 220 nm

S.No	Concentration µg/ml	Absorbance Mean±Standard Deviation
01	05	0.264
02	10	0.583
03	15	0.810
04	20	1.108
05	25	1.375

ISSN: 2519-9889
Impact Factor: 5.721

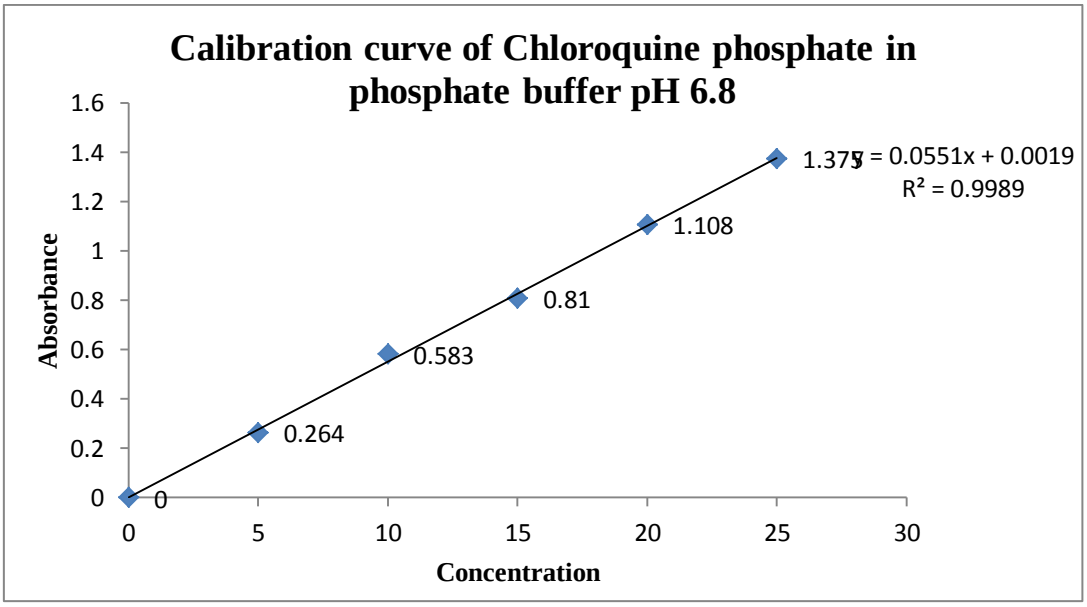

Figure- 3 Calibration curve of Chloroquine phosphate in phosphate buffer pH 6.8

Table No. 3: Absorbance data of chloroquine phosphate in phosphate buffer 7.4 for preparation of calibration curve

S.No	Concentration µg/ml	Absorbance Mean±Standard Deviation
01	05	0.296
02	10	0.538
03	15	0.813
04	20	1.037
05	25	1.331

ISSN: 2519-9889
Impact Factor: 5.721

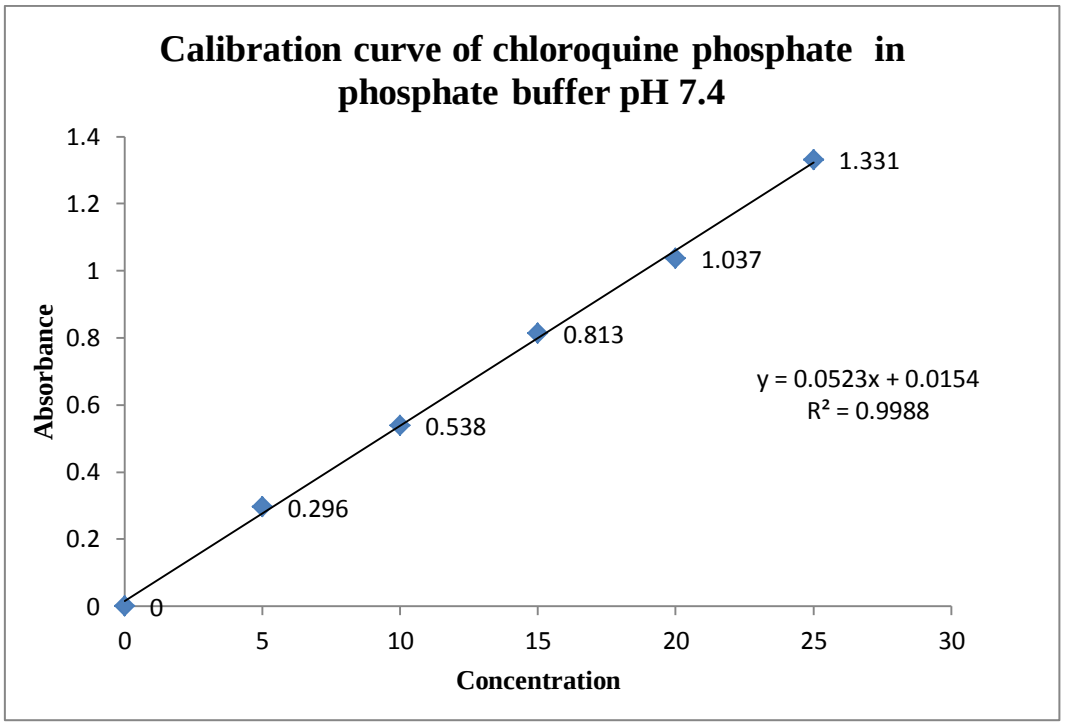

Figure-4 Calibration curve of Chloroquine phosphate in phosphate buffer pH 7.4

4.1.4 Determination of Partition coefficient:

The partition coefficient was found to be logP= 4.63. The partition coefficient found cleared that the drug is highly lipophilllic.

4.1.5 Determination of solubility of chloroquine phosphate in various medium:

The solubility of resveratrol in various mediums were studied and the results of study were shown in below table:

Table-7.4: Solubility data of chloroquine phosphate in different mediums

S.NO	Solvent	Solubility (mg/ml) Mean ± SD	Inference
01	Distilled water	300 ± 1 ml	Practically soluble
02	Phosphate buffer pH 6.8	280 ± 1 ml	Practically soluble
03	Phosphate buffer pH 7.4	290 ± 1 ml	Practically soluble

ISSN: 2519-9889
Impact Factor: 5.721

4.1.6 Drug-excipient interaction study

The drug chloroquine phosphate was found to be compatible with various excipients which were selected for formulation of TDDS. The compatibility was assessed by TLC and the retention factors of all ratios found similar.

Table-7.5: Data of drug-excipient interaction study

S.No	Drug/Drug + Excipient Ratio (1:1)	Initial appearance	Final appearance	Retention factor
01	Drug (Chloroquine phosphate)	White powder	White powder	0.55
02	Pure Drug + Gelatin	Light yellow	Light yellow	0.56
03	Pure Drug + Dibutyl phthalae	White transparent	White transparent	0.53
04	Pure Drug + Polyvinyl pyrolidone	White	White	0.58

4.2 Formulation and development:

Table-7.6: Formulation and development

S. No.	Name of Ingredients	F1	F2	F3	F4	F5	F6
1	Chloroquine Phosphate (mg)	100	100	100	100	100	100
2	Gelatin (mg)	200	250	300	350	400	450
3	PVP (mg)	200	300	350	250	450	400
4	Dibutyl Pthalate (%)	30	30	30	30	30	30

4.3 Evaluation of Transdermal Patch:

(1) Folding Endurance

Folding endurance is determined to identify flexibility of the films. Folding endurance was determined by folding the films repeatedly in the same part of the film until it broke.in this. (**Table-6)**

(2) Film Thickness

Five films from each formulation were selected randomly to study the thickness using thickness gauge and average was determined. .in this.(**Table-6)**

ISSN: 2519-9889
Impact Factor: 5.721

(3) Weight Variation Test

The study was carried out by determining weight of randomly selected five films from each batch with the help of high accuracy electronic balance. The average weight of a film and its standard deviation was calculated. .in this.(**Table-6)**

(4) Percentage of Moisture Content

Randomly selected films were weighed individually and kept in the platform of the dessicator containing anhydrous calcium chloride at room temperature for 24 hours.with respect to the final weight. .in this(**Table-6)**

(5) Drug Content Determination:

Selected film from each batch was put into a 100ml standard flask containing the buffer solution (pH - 7.4) and shaken continuously for 24 hours. Then the solution was filtered and drug content was determined with the help of UV spectrophotometer at wave m. length 220 nm. .in this(**Table- 6)**

Table-6: Data of Folding Endurance Thickness, Weight Variation, % Moisture content, % Moisture Uptake, Drug content.

Formulation Code	Folding Endurance	Thickness (µm)	Weight Variation (mg)	% Moisture Content	% Moisture Uptake	Drug Content
F1	98±4.28	160±3.03	10.6±0.37	2.32±0.56	1.83±0.42	97.9±2.42
F2	102±4.02	168±5.88	11.12±0.26	2.92±0.68	2.63±0.56	98.6±2.45
F3	96±6.03	170±5.95	10.23±0.36	4.02±0.89	3.63±0.35	97.5±2.41
F4	110±5.22	158±5.53	11.20±0.29	1.96±0.39	1.32±0.31	96.9±2.39
F5	103±5.00	166±5.81	10.73±0.35	1.78±0.33	1.25±0.26	98.8±2.45
F6	108±5.32	154±5.39	10.97±0.40	1.64±0.31	1.12±0.34	95.8±2.35

***(6)IN VITRO* DRUG PERMEATION STUDIES**

In vitro permeation studies were performed using Franz diffusion cell. The dialysis membrane (2x2cm) was mounted between the donor and receptor compartment of the diffusion cell. The dialysis sac was previously soaked for 2 h in PBS. The formulated films were placed over the membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 37 ± 20C.Samples were withdrawn (2 mL) at predetermined time intervals and replaced with an equal volume of phosphate buffer. The samples were suitably diluted and analyzed to determine drug content using UV spectrophotometer at a wave length of 220nm.

ISSN: 2519-9889
Impact Factor: 5.721

5. CONCLUSION: Transdermal therapeutic systems are high- tech patches that make treatment much more convenient and pleasant for patient .Instead of having to take lots of tablets, patients often only have to apply a new patch once a week In addition, patches from LTS also ensure a constant drug level for the entire duration of wear Symptoms upon getting up in the morning as a result of low drug levels during the night are avoided. There are five major advantages of transdermal patches above other systems like Improved well –being for patient, constant drug levels, fewer side effects, Drugs that cannot be absorbed via the gastrointestinal tract can now be used and because the substance is released evenly and directly into the blood stream, less of the substance may be required

In the application of delivery systems for the delivery of chloroquine is the design of the systems affects their therapeutic efficacy. In the design of polymer – drug conjugates for the delivery of chloroquine is the nature of targeting moieties affect the specificity of the conjugates , materials used influence their degree of toxicity, the type of drug linkers determine the drug release mechanism from the conjugates and the position of functionalities on the conjugates affect their rate of degradation. The design of micells influence their degree of toxicity, rate of biodegradation and the rate of diffusion of the incorporated drugs. However, some of these delivery systems are limited by aggregation upon storage, burst drug release effects and susceptibility of selected drug linkers to some enzymes resulting in rapid drug release. There are few reports on the delivery of Chloroquine is to form selected systems such as ethosomes, nanocapsules niosomes and CNTs indicating that there is a need for further investigations on these systems. Most of the systems were evaluated in vitro and in vivo and the results obtained were promising suggesting that there is a pressing need for further studies to be performed on these systems to reach clinical trials because emergence of drug resistance remains a global problem.

REFERENCES

[1]. Murambiwa, P Masola, B Govender, T Mukaratirwa, S Musabayane, C T (2011) Anti-malarial drug formulations and novel delivery systems: A review, Acta Tropica, 118, 71–79
[2]. Sharma, R.K., et al., *Malaria situation in India with special reference to tribal areas.* The Indian journal of medical research, 2015. **141**(5): p. 537.
[3]. Singh, K.K., *Nanomedicine in malaria*, in *Patenting Nanomedicines.* 2012, Springer. p. 401-434
[4]. Mayank P. Patel*, M. M. Gupta1 Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur (Rajasthan) India
[5]. Kesarwani, A., et al., *Theoretical aspects of transdermal drug delivery system.* Bulletin of Pharmaceutical Research, 2013. **3**(2): p. 78-89
[6]. Arora, P. and B. Mukherjee, *Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt.* Journal of pharmaceutical sciences, 2002. **91**(9): p. 2076-2089.
[7]. Elmowafy M , Elrehaily A , Elharby A, Ali T , Elelian A , Adel E Adel and Naif E Transdermal Drug Delivery Systems

ISSN: 2519-9889
Impact Factor: 5.721

[8]. Gaikwad, A.K., *Transdermal drug delivery system: formulation aspects and evaluation.* Comprehensive J Pharm Sci, 2013. **1**(1): p. 1-10.
[9]. Dhiman, S., T.G. Singh, and A.K. Rehni, *Transdermal patches: A recent approch to new drug delivery system.* Int J Pharm Pharm Sci, 2011. **3**(5): p. 26-34.
[10]. *Shingade GM1, Aamer Quazi1**,** Sabale PM2, Grampurohit ND2, Gadhave MV2, Jadhav SL2, Gaikwad DD2(2012) Review on recent trendn on transdermal drug delivery system, 2(1), 66-75
[11]. Latheeshjlal, L., et al., *Transdermal drug delivery systems: an overview.* Int. J. PharmTech Res, 2011. **3**(4): p. 2140-8.
[12]. Ghulaxe, C. and R. Verma, *A review on transdermal drug delivery system.* The Pharma Innovation Journal, 2015. **9**(1): p. 37-43.
[13]. Mistry, R.B. and N.S. Sheth, *A review: self emulsifying drug delivery system.* Int J Pharm Pharm Sci, 2011. **3**: p. 23-8.
[14]. Wiliams,A 2003 Transdermal and topical drug delivery published by the pharmaceutical press
[15]. Clara Luisa Domínguez-Delgado1, Isabel Marlen Rodríguez-Cruz1 and Miriam López-Cervantes1,2
[16]. Lembhe,s and Dev, A 2016 trasdermal drug delivery system, an overview world journal of pharmacy and pharmaceutical sciences 5(7)
[17]. Mayorga, P., et al., *Research Note Rodent malaria prophylaxis by transdermal delivery of primaquine.* International journal for parasitology, 1998. **28**(8): p. 1283-1285
[18]. Walters , K A (2002) Dermatological and transdermal formulations, Published by Taylor and Francis Group LLC CRC Press, 119, 94
[19].) https://www.rxlist.com/aralen-drug.htm#description
[20]. Raymod Rowe Paul J. Sheskey Marian E Quinn (2009) Handbook of pharmaceutical Excipients, published by the pharmaceutical press (6) 278
[21]. Raymod Rowe Paul J. Sheskey Marian E Quinn (2009) Handbook of pharmaceutical Excipients, published by the pharmaceutical press (6)225-226
[22]. Raymod Rowe Paul J. Sheskey Marian E Quinn (2009) Handbook of pharmaceutical Excipients, published by the pharmaceutical press (6) 283-284-285
[23]. Raymod Rowe Paul J. Sheskey Marian E Quinn (2009) Handbook of pharmaceutical Excipients, published by the pharmaceutical press (6) 581-582-583-584-585
[24]. Patel J, Dhingani A, Garala K, Raval M, and Sheth N (2013) Quality by design approach for oral bioavailability enhancement of Irbesartan by selfnanoemulsifying tablets. Informa Healthcare USA, Inc.,volume -2013, 1-24.
[25]. Aulton M. E., Pharmaceutics the science of dosage form design. 2nd edition Churchil livingstone; 136-137.
[26]. Kharat R S and Bathe R S / International Journal of Biomedical and Advance Research 2016; 7(4): 147-159.
[27]. Srivastava A*,. Patel A K,. Prasad R K, A. K. Sahu and S. S. GautamShambhunath Institute of pharmacy, Jhalwa, Allahabad, U. P.-211012.

