International Journal for Pharmaceutical Research Scholars (IJPRS)

V-5, I-2, 2016 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Fabrication and Evaluation of Transdermal Patches of Primaquine Phosphate

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Manuscript No: IJPRS/V5/I2/00085, Received On: 20/05/2016, Accepted On: 24/05/2016

ABSTRACT

Fabrication and Evaluation of matrix type Transdermal Patches of Primaquine Phosphate with different ratio of eudragit-L100 and S-100 combination by the solvent evaporation technique. All the patches have been evaluated for their Physiochemical properties was studied by infrared Spectroscopy. Formulation F1 was found best among the all formulation on basis maximum in-vitro release, drug content and folding endurance i.e. 4.711, 99% ± 0.2, 26 ± 2. Other parameters like moisture content, moisture uptake, surface pH was found 1.32 ± 0.38, 3.14 ± 0.2 and 8.9 respectively. Hence F1 formulation was used to incorporate penetration enhancer labrafac™ PD, labrafil® 1944CS and lauroglucol™ FCC. By using this three penetration enhancer nine formulation L1 to L9 was fabricated to increasing volume of 0.5ml, 1.0ml, 1.5 ml. All the formulation was tested for thickness, weight variation, folding endurance, surface pH, moisture content and %drug content. L6 was showing maximum drug content and folding endurance as 99.8%, 28 respectively. The in-vitro release study was carried out with Shimadzu HPLC system. L6 formulation showed the best release value 75.47% in 24hr, emerging to be ideal formulations for Primaquine Phosphate and the mechanism of release was fitted to peppas kinetic models. The formulated transdermal patches increase antimalarial activity and reduced the adverse drug reactions gastrointestinal distress, nausea and methemoglobinemia with cyanosis.

KEYWORDS

Primaquine Phosphate, EudragitL-100, EudragitS-100, Solvent Casting Technique, Plasticizer, Different enhancer

INTRODUCTION

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action[1]. 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. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time, and offer many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, decrease in frequency of administration, reduction in gastrointestinal side

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effects and improves patient compliance. TDDS is ideally suited for diseases that demand chronic treatment[4].

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-life and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of novel drug delivery system such as transdermal drug delivery systems, controlled release systems, transmucosal delivery systems etc., are emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.

Primaquine is an antimalarial agent and is the essential drug treating *P. vivax* of malaria. In the blood, malaria parasites break down a part of the red blood cells known as haemoglobin. When this happens haemoglobin is divided into two parts; haem and globin. Haem is toxic to the malaria parasite. To prevent it from being damaged, the malaria parasite produces a chemical which converts the toxic haem into a non-toxic product. Primaquine acts by interfering with a part of the parasite (mitochondria) that is responsible for supplying it with energy. Without energy the parasite dies. This stops the infection from continuing and allows the person to recover. Primaquine kills the intrahepatic form of *Plasmodium vivax* and *Plasmodium ovale*, and thereby prevents the development of the erythrocytic forms that are responsible for relapses (it also kills gametocytes). Primaquine has gametocytocidal activity against all plasmodia, including *P. falciparum*. Primaquine mechanism of action is not well understood. It may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite. Also, although its mechanism of action is unclear, primaquine may bind to and alter the properties of protozoal DNA. Primaquine is readily absorbed after oral ingestion. It is oxidized in liver with a plasma $t_{1/2}$ of 3.4-7.4 h and excreted in urine within 24 h.

MATERIAL AND METHODS

Materials

Primaquine phosphate was received as a gift samples from Merck specialities Pvt. Ltd. (Mumbai, India).Eudragit L-100and Eudragit S-100 were acquired from Evonik rohm pharma polymer (Germany). Polyethylene glycol (PEG-400) was acquired from Ozone internation. Labrafac, Labrafil, Lauroglycol were Gattefosse India Pvt. Ltd (Mumbai, India).Distilled water was used throughout the study.

Examination of Compatibility Study of Drug and Polymer

Compatibility study between Primaquine phosphate and polymers was studied by using differential Scanning calorimetry (Perkin Elmer). DSC is a thermal analysis technique. A sample of known mass is heated or cooled and change in its heat capacity is tracked as change in heat flow. DSC study of pure drug is showing endotherm graph at 209.62ºC. Drug and EudragitS-100and Eudragit L-100 (1:1) compound thermo-gram, and observed that no physiochemical change in drug peak.

Fabrication of Transdermal Patches

Matrix type transdermal patches of primaquine phasphate were prepared by the solvent evaporation technique. The polymers namely Eudragit S-100 and Eudragit L-100 were accurately weighed and dissolved in the solvent system consisting of Methanol: Dist. Water (9:1). Propylene glycol 0.04ml was dispersed under constant stirring with a magnetic stirrer and the resultant homogeneous solution was poured into a Petridis. Controlled solvent evaporation at room temperature was achieved by inverting a funnel over the Petridis to obtain matrix type transdermal patches. The dried patches were wrapped in aluminium foil and kept in dessicator until used. After that Best patch was selected on the basis of all evaluated parameter such as, thickness, Folding endurance, Drug content, Moisture content moisture uptake Surface pH, *in-vitro* drug release and incorporated of penetration enhancer with different concentration(Labrafac PG, Lauroglycol FCC, Labrafil M 1944).

Table 1: Composition of Transdermal patches

Sr. No.	Ingredients	Formulation Code				
		F1	F2	F3	F4	F5
1	Drug (mg)	225	225	225	225	225
2	Eudragit-S100: Eudragit-L100	1:1(400)	2:1(400)	1:2(400)	3:2(400)	2:3(400)
3	Propylene glycol ml	0.04	0.04	0.04	0.04	0.04
4	Methanol: water (9:1)ml	10	10	10	10	10

Table 2: Incorporation of Penetration Enhancer

Penetration Enhancer								
Labrafac PG			Lauroglycol FCC			Labrafil M 1944		
0.5ml	1ml	1.5ml	0.5ml	1ml	1.5ml	0.5ml	1ml	1.5ml

Table 3: Fabrication of transdermal patches with penetration enhancer

code	Penetration Enhancer	Drug ml	EudragitL100: EudragitS100	Propylene glycol ml	Penetration Enhancer Ml	Methanol: water (9:1)ml
L1	Lauroglycol	225	1:1(400)	0.04	0.5	10
L2	Lauroglycol	225	1:1(400)	0.04	1.0	10
L3	Lauroglycol	225	1:1(400)	0.04	1.5	10
L4	Labrafac	225	1:1(400)	0.04	0.5	10
L5	Labrafac	225	1:1(400)	0.04	1.0	10
L6	Labrafac	225	1:1(400)	0.04	1.5	10
L7	Labrafil	225	1:1(400)	0.04	0.5	10
L8	Labrafil	225	1:1(400)	0.04	1.0	10
L9	Labrafil	225	1:1(400)	0.04	1.5	10

Evaluation of Transdermal Patches

Appearance, Size, Shape and Thickness

The formulated patches were checked for their appearance, shape and thickness. The thickness of patches was determined at five different places using a micrometer screw gauge (Mitutoyo Co., Japan) for each formulation and mean value was calculated[26].

Weight Variation

The patches were subjected to mass variation by individually weighing on digital weighing balance (Sartorius, BSA2245-CW) and randomly selected patches. The average of five observations of each formulation was calculated. Such determinations were carried out for each formulation[32].

Folding Endurance

It was determined by repeatedly folding a small strip of the patch (1cm^2) at the same place till it broke. The number of times a patch can be folded at the same place without breaking gave the value of folding endurance. Further, less folding endurance gives more brittle[33].

Surface pH

Surface pH of the patches was determined by the method described by Botten berg et al. The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour 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 minute[34].

Percentage of Moisture Content

The patches of (1cm^2) were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hours. Individual patch were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to initial weight[19].

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} X\ 100$$

Percentage of Moisture Uptake

The patches were weighed accurately and placed in desiccators containing 200 ml of saturated solution of potassium chloride (84% relative humidity) at room temperature. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. The test was repeated in triplet[16].

$$\text{Percentage moisture uptake} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} X\ 100$$

Drug Content

The patch of specified area (1 cm^2) was cut and added to a volumetric flask containing 100 ml of phosphate buffer pH 7.4. The medium was stirred in a magnetic stirrer for proper dissolution for 6 hours. The contents were filtered using Whatman filter paper and the filtrate was analyzed by HPLC system (Shimadzu Japan UFLC-20AD) at 265 nm. The experiment was performed in triplicate[35].

In-vitro Skin Permeation Studies

- *Introduction:* The animal study protocol was duly approved by the animal ethical committee Hygia/M.Pharm/30 /2012-2013.
- *Preparation of Skin:* In this study used albino rats (weighing between 200-250 g) were purchased from central drug research institute, Lucknow. Rat was sacrificed by cervical dislocation and skin removed using with the help of scalpel and scissor. Hair was removed with an electric clipper and small hairs were removed with hair removal cream.
- *Frinz diffusion cell:* The *in-vitro* skin permeation studies were carried out on a Franz diffusion cell with a donar and receptor compartment. capacity of receptor was 10 ml.

Method

- The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4.
- The excised skin was mounted between the receptor and donor compartment of the

diffusion cell. 1 cm diameter of formulated patch was placed in intimate contact with the stratum corneum side of the skin and the donor compartment was kept in contact with the receptor compartment.

- The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was continuously stirred.
- The temperature was maintained at 37±2°C throughout the experiment.
- The samples of 0.3 ml were withdrawn at different time interval of 0, 1, 2, 4, 8, 10, 12, 16, 20 and 24 hrs. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions.
- Analyzed for drug content HPLC method at 265 nm. The cumulative percentages of drug permeated were plotted against time[36].

RESULTS AND DISCUSSION

Compatibility Studies of Drug and Polymer

DSC of Primaquine Phosphate with Polymer Eudragit L-100 and Eudragit S-100 with drug.

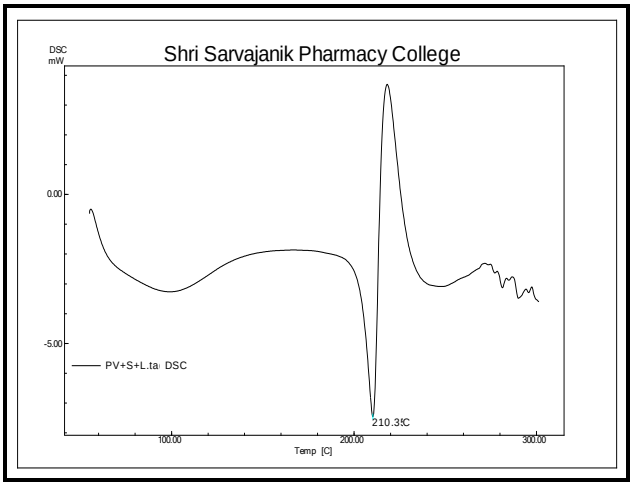

Figure 1: Compatibility Studies of Drug and Polymer

Evaluation of Transdermal Patches

Table 4: Physiochemical Characterization of PQP patches without Penetration Enhancer

S. No.	Code no.	Thickness (mm)	Wt. uniformity	Folding Endurance	Surface pH	Moisture content	Moisture uptake	Drug content
1.	F1	0.23±0.4	90.9±0.6	26± 2	8.9	1.32±0.38%	3.14 ± 0.2%	99 ± 0.2%
2.	F2	0.24±0.2	85.4±1.4	19±4	8.4	2.30±0.61%	1.47 ± 0.5%	94 ± 0.5%
3.	F3	0.35±0.2	94.5±1.2	21±2	8.8	1.57±0.72%	2.84 ± 0.3%	95 ± 0.3%
4.	F4	0.26±0.4	89.4±1.7	18±3	8.5	2.10±0.29%	3.63 ± 0.2%	97 ± 0.2%
5.	F5	0.43±0.9	95.3±0.8	23±5	8.3	2.13±0.51%	3.85 ± 0.3%	98 ± 0.2%

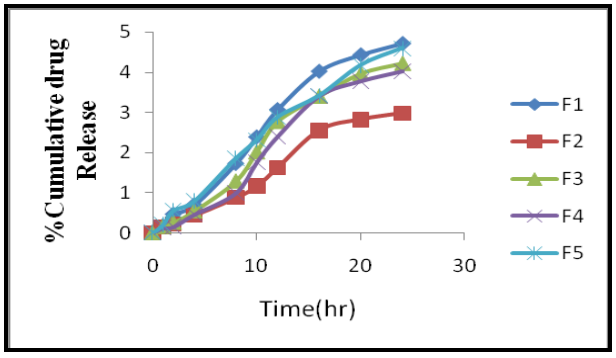

Figure 2: *In-vitro* skin permeation studies of five Formulations without PE

Table 5: *In-vitro* skin permeation studies of five Formulations without Penetration Enhancer

S. No	Time(hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
1.	0	0	0	0	0	0
2.	1	0.173	0.146	0.156	0.123	0.204
3.	2	0.461	0.211	0.260	0.154	0.565
4.	4	0.693	0.439	0.545	0.460	0.796
5.	8	1.725	0.878	1.290	0.995	1.856
6.	10	2.385	1.163	2.015	1.757	2.315
7.	12	3.063	1.624	2.776	2.399	2.882
8.	16	4.020	2.555	3.402	3.411	3.417
9.	20	4.428	2.825	3.966	3.783	4.174
10.	24	4.711	2.980	4.222	4.029	4.598

Table 6: Physiochemical Characterization of Patches with Penetration Enhancer

Code	Thickness (mm)	Wt. variation	Folding endurance	Surface pH	Moisture content	Moisture uptake	%Drug content
L1	0.33±0.4	85.41±0.6	25±4	8.4	2.99±1.5	3.5±1.2	85.2%
L2	0.46±1.7	82.61±0.3	26±2	8.1	3.21±1.8	3.7±0.8	83.5%
L3	0.38±0.7	78.5±0.8	24±5	8.7	3.5±0.9	4.1±0.5	88.4%
L4	0.24±0.1.5	69.8±1.4	20±3	8.6	3.85±1,2	3.8±1.5	90.5%
L5	0.42±1.2	80.1±0.5	22±2	8.5	3.92±1.3	3.2±1.6	91.%
L6	0.28±0.8	70.58±1.2	28±4	9.4	2.46±0.5	1.68±0.9	99.8%
L7	0.37±1.1	65.9±1.7	23±4	8.8	2.8±1.9	2.7±0.7	87.8%
L8	0.26±1.8	68.6±1.3	27±3	9.2	2.95±1.8	3.6±1.2	89.5%
L9	0.21±0.6	72.3±1.6	22±2	8.7	3.8±1.7	3.9±1.7	92.7%

Table 7: *In-vitro* Release of Transdermal patches with Penetration Enhancer

Time (hr)	%Drug release									
	Lauroglycol			Labrafac			Labrafil			Without PE
	L1 (0.5)	L2 (1.0)	L3 (1.5)	L4 (0.5)	L5 (1.0)	L6 (1.5)	L7 (0.5)	L8 (1.0)	L9 (1.5)	F1
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.78	0.90	0.88	0.87	0.97	1.00	0.69	0.78	0.81	0.17
2	0.92	1.12	1.74	1.61	1.83	2.01	0.91	0.88	1.12	0.46
4	1.16	2.42	3.97	2.25	2.59	2.91	1.18	1.15	1.48	0.69
8	6.18	7.02	10.25	8.78	9.93	10.40	5.05	4.07	7.23	1.73
10	10.75	10.95	17.54	17.03	15.09	20.09	8.63	10.51	13.71	2.39
12	16.50	21.67	28.56	22.31	27.22	37.69	12.38	23.48	25.60	3.06
16	31.69	32.33	41.36	40.52	47.99	51.97	18.22	29.44	37.31	4.02
20	36.60	44.31	46.55	54.43	65.73	67.85	31.48	38.81	41.02	4.43
24	40.04	47.37	49.82	60.86	71.20	75.47	34.90	43.04	45.39	4.71

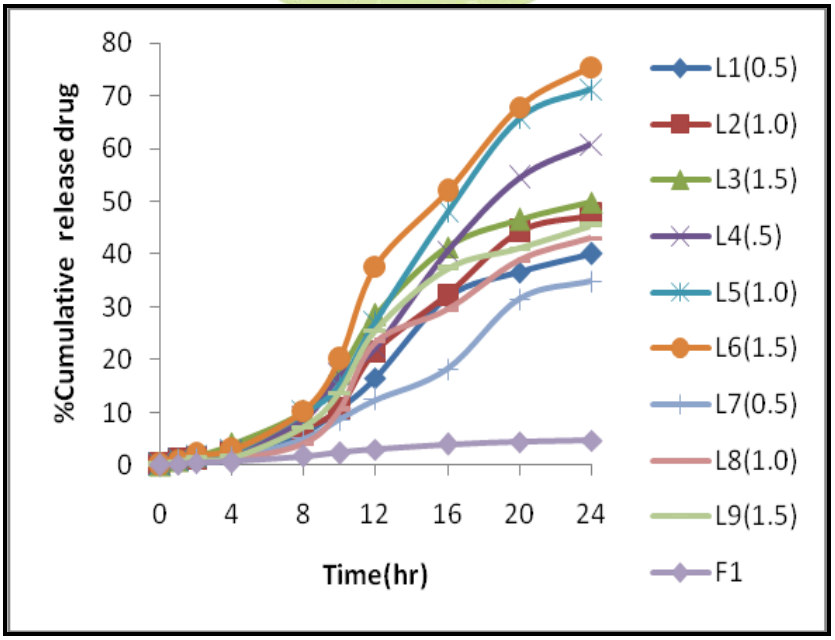

Figure 3: %Cumulative Drug release of Patch

Physical Appearance

The physical appearance of all these patches was evaluated. All the patches were found to be uniformly yellowish in color, smooth, flexible, and homogenous.

Thicknesses

The thickness of the films varied from 0.21±0.6 to 0.46±1.7mm.The values obtained for all the formulation is given the table 6.

Weight Uniformity

The weight uniformity has been found to be in the range of 65.9±1.7 to 85.41±0.6 mg. The values for all the formulations are tabulated in the table 6.

Folding Endurance

The folding endurance were found to be in range of 20±3 to 28±4. The value for all nine formulation is given in table 6.This data revealed that the patches had good mechanical strength along with flexibility.

Surface pH

The surface pH was found to be in the range of 8.1 to 9.4. The values for all formulation are given in table 6.

Moisture Content

Moisture content study was conducted on all the formulation. It was observed that L6 showed lowest percentage 2.46±0.5 moisture content when compared to formulation. The value for the moisture absorption has given in table 6.

Moisture Uptake

Moisture uptake study was conducted on all formulation and observed that L6 showed lowest percentage 1.68±0.9. All the values have given in table 6.

%Drug Content

The percentage of drug content in various formulations ranged from 83.5% to 99.8% given in table 5.9.L1 to L9 formulation was carried out for *in-vitro* drug release and below *in-vitro* Table 7 was discussed.

***In-vitro* Release Study**

This study was carried out by diffusion process containing donor and receptor compartments using 7.4 pH Phosphate buffer media. Values of release data obtained from formulation are tabulated in table 7 and Figure 3 Shows the plots of cumulative % drug released as function of time for different formulation with their different enhancer. Without enhancer formulation F1 was0.17% drug release at 1 hr., but different enhancer such as lauroglycol in high con. Was L3 0.88%, labrafac in high con L6 was 1% and Labrafil in high con L9 was 0.97% at 1 hr. After 24 hr., without enhancer formulation F1 was 4.71 but with penetration lauroglucol L3, Labrafac L6 and Labrafil L9 were 49.83%, 75.47%, 45.39% respectively. Hence F1 drug release was the 4.71% which was increased by incorporate the various concentration of the penetration enhancer. In all formulation L6 drug release was the best release from other formulation.

Table 7: Curve fitting data of release profile for designed formulation

Formulation	Korsmeyer-Peppas Model	
	R^2	n
L1	0.9610	1.388
L2	0.9715	1.429
L3	0.9614	1.153
L4	0.9820	1.478
L5	0.9734	1.529
L6	0.9718	1.376
L7	0.9844	1.614
L8	0.9553	1.404
L9	0.9503	1.246
F1	0.9781	0.886

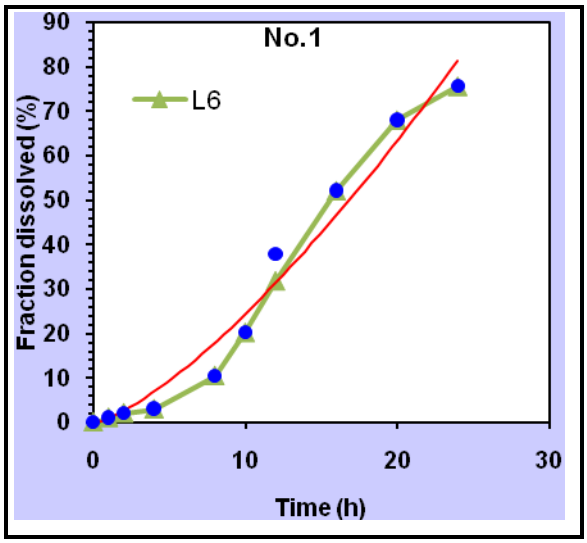

Figure 4: Kinetic Releases of L6 formulation

DISCUSSION

Primaquine Phosphate in combination with Eudragit S-100 and Eudragit L-100 and Propylene glycol with incorporation of penetration enhancers Lauroglycol, Labrafac, Labrafil and produced smooth, flexible and transparent films. DSC studies indicated there was no interaction between Primaquine Phosphate and polymers used. Primaquine Phosphate patches were fabricated and evaluated with combination of polymers and penetration enhancers. From the results, it was observed that thickness, weight variation, low moisture loss, low moisture absorption, tensile strength were suitable for maximum stability of the prepared formulations. The drug content and in-vitro drug release rate increases with penetration enhancer labrafac 1.5 ml. The percentage drug content for L6 was found to be 99.8% and drug release 75.47 at 24 h. The drug release kinetics studies formulation L6 follows zero order.

CONCLUSION

In conclusion, controlled release TDDS patches of Primaquine Phosphate can be fabricated using the polymer combinations Eudragit S-100 and L-100, with penetration enhancer labrafac™ PD, labrefil® 1944CS and lauroglucol™ FCC and PEG-400 as plasticizer. The release rate of drug through patches increased when the concentration of penetration enhancer labrafac was increased. The drug release kinetics formulation L6 showing zero order release kinetics (Table 5). Further, *in vivo* studies have to be performed to correlate with *in vitro* release data for the development of suitable controlled release patches for Primaquine Phosphate.

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