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DESIGN, FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES FOR AN ANTIHYPERTENSIVE DRUG

Murhula Mongane Pascal*[1], B. Prakash Rao[1], Usha GK[1], Rama Mogar[1], Twinkle Sigh[1,]
[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Karnataka college of Pharmacy
#33/2, Thirumenahalli ,Hedgenagar Main road, Bangalore - 560064, India.
Email: murhulamongane@gmail.com

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Abstract

The objective of this work was to formulate and evaluate a matrix type transdermal film of anti-hypertensive drug by using EUDRAGIT RSPO and RLPO as polymers in order improve the drug's bioavailability. The matrix-type transdermal films of Labetalol were prepared by solvent casting method using Eudragit RSPO and RLPO as polymers; PEG-400 as a plasticizer, DMSO as a penetration enhancer and aluminium foil as a backing membrane in various proportions.

The compatibility study was performed by FTIR. The prepared patches were tested for their thickness, drug content uniformity, moisture content, moisture uptake, folding endurance, In-vitro release studies and stability studies were performed on the optimized formulation. The FTIR spectra indicates there is no interaction between Labetalol and polymers. Formulations' thickness varied from 0.21 to 0.29 mm and the drug content uniformity from 94.6 to 99.03%. The moisture content was found to increase with increasing concentration of lipophilic polymer. Moisture uptake of the formulations varied from 3.36 to 1.25%. Folding Endurance (95 to 123) increases with increase in the Eudragit proportion. Formulation F8 and F9 exhibits 95% and 97% of drug release. The results obtained indicated a potential control release of labetalol transdermal patches. Stability studies indicates that there were no significant changes in physicochemical parameters of F3 formulation.

Keywords: Eudragit-RLPO, Eudragit RSPO, *In-vitro* permeation, Labetalol, transdermal patch.

Introduction

Transdermal Drug Delivery System (TDDS) is categorised under the controlled drug delivery, in which the objective is the drug delivery the through skin in a predetermined and controlled rate [1]. The delivery of drug

by transdermal route have several advantages than conventional dosage forms which include the avoidance of first-pass metabolism, the reduced bioavailability, dosing inflexibility and dose dumping[1] .

The success of a dermatological drug that must be used for systemic drug delivery will depend on the drug's ability to penetrate through the skin in sufficient quantity to achieve the desired therapeutic effect[2]. The potential risk factors of hypertension are excessive alcohol consumption, tobacco, high salt intake, smoking, sedentary lifestyle, and increasing BMI[3,4].

Hypertension is usually defined as the pathological elevation of arterial Blood Pressure. The hypertension diagnosis is made when the average of two or more diastolic Blood pressure measurements on at least two subsequent visits is greater or equal to 90 mm Hg or when the average of multiple systolic Blood Pressure readings on 2 or more subsequent visits is consistently greater or equal to 140 mm Hg[5].

Labetalol is alpha and Beta non-selective blocker of the adrenergic receptors. Competitively it binds with these receptors and then the proliferation of cardiovascular symptoms is inhibited (e.g. hypertension). After oral administration this drug is rapidly absorbed and after 100 mg oral dose, peak plasma concentrations are reached 20-60 min.

The plasma half-life is 3.5 hours which is the base of a compulsory frequent dosing in case of conventional formulations, which invariably leads to poor patient compliance.

Labetalol undergoes a high hepatic first pass metabolism (60-75 %) leading to poor bioavailability on oral administration. With a low molecular weight (364.9), labetalol is sufficiently lipophilic (partition coefficient in octanol/water is 7.08) with favourable hydrophilicity (solubility in water is >1 in 30).

All these factors indicates that labetalol might be a good choice as a candidate drug for transdermal delivery. Hence we propose matrix TDDS of labetalol for hypertension management[6].

Materials and Methods

Materials

Labetalol was gifted sample from Yarochem pvt ltd, Mumbai, India. Eudragit RSPO and Eudragit RLPO were purchased from Evonik Degusa (P) Ltd, India.

PEG-400 was procured from Karnataka fine chem, bangalore, India. DMSO was gifted from Yarochem pvt ltd, Mumbai, India.

Methods

Preformulation studies

Infrared (IR) absorption spectroscopy

To investigate any possible interaction between the drug and the utilized polymers (Eudragit RLPO, RSPO), IR spectrum of pure drug (Labetalol) and its physical mixture was carried by using FTIR the range selected was from 400cm-1 to 4000 cm-1.

Solubility determination: In distilled water and phosphate buffer of pH 7.4 were used to determine the solubility of the drug using standard method.

Excess amount of the drug was taken and dissolved in an amount of above solvents separately in a glass beaker to get a saturated solution. This solution was shaken intermittently to assist the attainment of equilibrium with the undissolved drug particles. Then the filtered drug solution was withdrawn after 24hrs and successively diluted with respective solvents and the concentration was measured spectrophotometrically. Averages of triplicate readings were taken.

Melting point determination

To determine the Melting point of the drug a small amount of the drug was taken in a capillary tube closed at one end and was placed in the Melting point apparatus called Thiel's melting point apparatus and the temperature at which the drug melts was noted. Averages of 3 readings were taken.

Partition coefficient

A solution of drug (1mg/ml) was prepared in n-octanol. 25ml of this solution was taken in a separating funnel and shaken with an equal volume of pH 7.4 phosphate buffer (aqueous phase) for 10 minutes and allowed to stand for 2 hours. Then aqueous phase and organic phase were separately collected and centrifuged at 2000 rpm. The 2 phases were analyzed by U.V. spectrophotometer for the drug concentration. Partition coefficient was determined by taking the ratio of the drug concentration in n-octanol to drug concentration in aqueous phase. Triplicate readings were taken

Permeability coefficient

The equation called "Potts and Guy equation" was used to calculate the permeability coefficient.

$$\textbf{Log Kp = - 2.7 + 0.71 x log Ko/w - 0.0061 x Molecular weight}$$

Where, Log Kp = Permeability coefficient and Ko/w = Partition coefficient.

Preparation of transdermal films

The matrix-type transdermal films containing Labetalol were prepared by solvent casting method. Eudragit RSPO and RLPO were used as polymers in the preparation of transdermal films. PEG-400 was used as a plasticizer, DMSO was used as a penetration enhancer and aluminum foil was used as backing membrane[7,8,9]. Weighed required quantity of polymers and dissolved in 4 ml of solvent mixture consisting of 1:1 ratio of Dichloromethane and Ethanol. This solution was kept a side for swelling. Then required quantity of plasticizer and drug solution were added and vortexed for 10 minutes. Further, it is set-a side for some time to exclude any entrapped air and is then poured on to the mercury surface in a Petri plate and this was kept a side for evaporation of solvent. The rate of solvent evaporation was controlled by inverting a glass funnel over the Petri plate. After overnight, the dried films were cut into a 2 cm^2 piece and stored in desiccators until further use.

Evaluation:

Physical appearance

The formulated transdermal patches were visually checked for color and clarity

Weight Variation

Weight variation was studied by individually weighing 3 randomly selected films. Such determination was performed for each formulation[10,11].

Film Thickness

The thickness of films was measured at three different places using a Screw gauge and mean values were calculated[10,11].

Folding Endurance

Folding endurance test was carried out by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance values[10]

Drug Content uniformity in the Film

The drug distribution uniformity was evaluated by determining drug content of the film by a spectrophotometric method. A known weight of film was dissolved and diluted subsequently with ethyl

alcohol and the concentration of Labetalol was spectrophotometrically measured at 302 nm against the blank ethyl alcohol solution containing the same amount of polymer and plasticizer without drug[10].

Percentage of Moisture Content

The individual weigh of film was taken and kept in desiccator containing activated silica at room temperature for 24 h. The films were weighed individually and 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 final weight[12].

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Percentage of Moisture Uptake

A weighed film was kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminium chloride) in a desiccator until a constant weight of film is obtained.

The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight[12].

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

In Vitro Drug Diffusion Studies

In vitro diffusion studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 140 ml by keeping the dialysis membrane between the donor and receptor compartment of the diffusion cell the dialysis membrane .The film was placed on cellulose acetate membrane and covered with aluminium foil.

The diffusion cell's receptor compartment was filled with phosphate buffer pH 7.4. All this assembly was fixed on a hot plate magnetic stirrer, and solution in the receptor compartment was constantly and continuously stirred using magnetic beads and the temperature was mentioned at 37 ± 0.5°C.

The samples were withdrawn at different time intervals and analysed for drug content spectrophotometrically. The receptor phase was refilled with an equal volume of phosphate buffer at each sample withdrawal[12,13,14].

Stability Studies

Stability testing is done in order to get evidence on how the quality of drug product varies with time under the environmental factors influence such as humidity, temperature and light. The stability studies is also important as it establish a retest period for the drug substance or the drug product shelf life and recommended storage conditions.

Stability studies were carried out on the films of the satisfactory formulation according to the ICH guidelines Q1C. The satisfactory formulation was stored in sealed aluminium foil and then kept at a room temperature for a period of 3 months. Films were evaluated for physical characteristics[15].

Results and Discussion

Preformulation studies

Drug Physicochemical properties

The results obtained from Preformulation studies are shown in table 3 from where the drug melting point was found to be 201.5 ^{0}C, solubility in water and in pH 7.4 phosphate buffer were 0.588 and 0.125 respectively. The partition coefficient was examined using n-octanol and phosphate buffer (pH 7.4) as they are considered to be the standard system for partition coefficient test; the amount of drug in the aqueous phase was found to be 61.42 mg/ml and 39.88mg/ml in octanol. 3.09 is the partition coefficient logarithmic value which indicated that the drug has sufficient lipophilicity to be formulated into transdermal patch.

Table 3: Preformulation studies of Labetalol.

S.No	Drug	Melting Point	Solubility (mg/ml)		Partition coefficient (P)		Log P
			Water	Buffer pH 7.4	Aqueous Phase (mg/ml	Octonolol (mg/ml)	
1	Labetalol	201.5	0.588	0.125	61.42	39.88	3.09

Fourier Transform Infra-Red studies (FTIR)

The spectrum obtained from FT infrared spectroscopy studies at wavelength from 4000 cm^{-1} to 400 cm^{-1} are shown in Figures 1 and 2. Characteristic peaks in the region of 3176.56 cm^{-1}, 1673.27 cm^{-1}, 1640.95 cm^{-1} (Table 2) were observed in physical mixtures which were identical to that of the pure drug; this confirmed the intactness of the drug in the physical mixture.

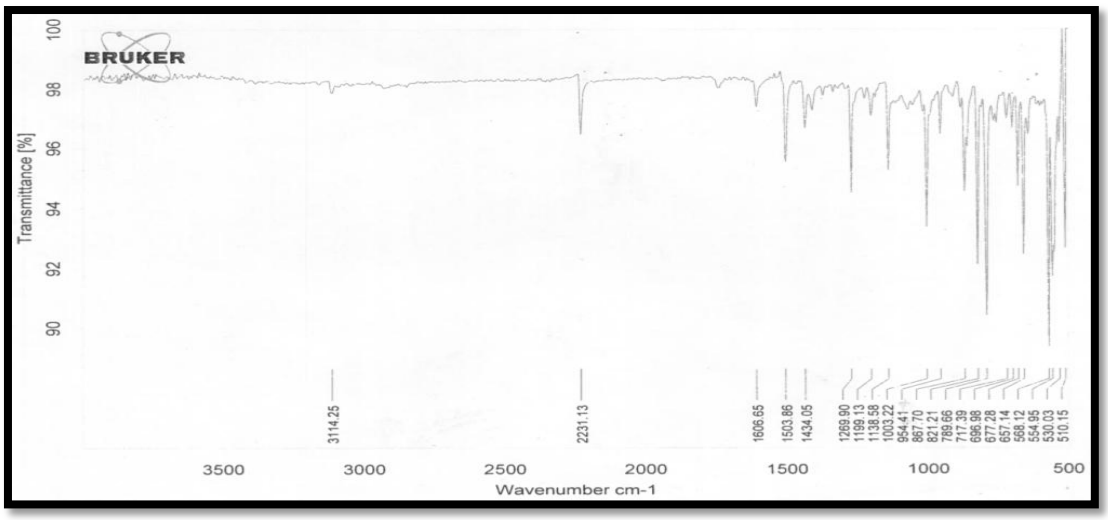

Fig. 1: FTIR Spectrum of Pure Labetalol.

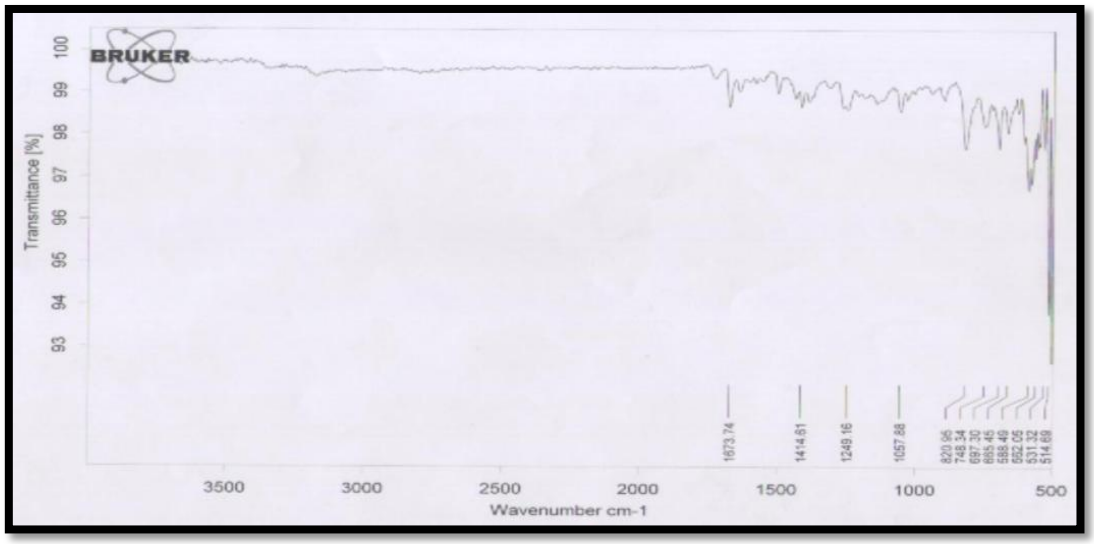

Fig. 2: FTIR Spectrum of physical mixture of drug with Eudragit-RSPO.

Characterization of formulations

Physical appearance

The Labetalol transdermal patch was prepared by using the rate controlling polymers (RSPO, RLPO) in proportion shown in Table 1. The physical appearance of the developed patches was translucent and not sticky.

Table 1: Formulation chart of Labetalol transdermal films.

Formulation Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug (mg)	168.8	168.8	168.8	168.8	168.8	168.8	168.8	168.8	168.8
Eudragit RSPO (mg)	160	200	160	200	200	120	120	160	120
Eudragit RSPO (mg)	120	120	160	160	200	120	160	200	200

PEG-400 (ml)	0.75	1	1	0.5	0.75	0.5	0.75	0.5	1
DMSO (ml)	1	0.75	0.5	1	0.5	0.5	0.75	0.75	1
Solvent (ml)	4	4	4	4	4	4	4	4	4

Table 2. FTIR study of drug and physical mixture of drug-polymer.

Bond/ Wavenumber(cm-1)	C=O stretching	C=O-OH stretching	NH stretching
Pure drug	1672.79	1639	3175.21
Drug + Eudragit RSPO	1673.27	1640.95	1640.60
Drug + EudragitRLPO	3175.21	3176.56	3174

Weight Variation

The weight of the formulations was found to be uniform as shown in table 4 and evinced by the SD values; it varied from 0.232 ± 0.047 to 0.340 ±0.003 mg per patch (n=3).

Table 4: Physicochemical parameters of prepared formulations F1-F9.

Formulation code	Weight variation(mg)	Film thickness(mm)	Folding endurance	% Content uniformity	% Moisture content	% Moisture uptake
F1	267±0.043	0.27 ± 0.01	103± 0.9	95.6± 2.5	2.13 ± 1.42	1.21 ± 1.58
F2	308± 0.026	0.21 ± 0.03	116 ± 2.1	96.5± 7.6	1.98 ± 2.42	1.59 ± 1.01
F3	301± 0.068	0.24 ± 0.06	107 ± 10	97.6± 2.9	1.99 ± 0.53	1.67 ± 0.44
F4	344±0.005	0.21 ± 0.01	114± 4	95.7± 5.6	1.84 ± 0.31	1.25 ± 2.07
F5	384 ±0.01	0.29 ± 0.04	123 ± 2	97.0± 0.9	1.15 ± 1.25	3.66 ± 0.96
F6	232± 0.047	0.20 ± 0.04	97 ± 7	99.1 ± 6.8	1.67± 0.37	1.65 ± 1.29
F7	273±0.015	0.17 ± 0.01	114 ± 1.5	96.8± 4.6	1.59 ±1.27	1.25 ± 2.42
F8	340±0.030	0.21 ± 0.01	108 ± 3	98.3± 5.8	1.54± 0.61	1.34 ± 0.91
F9	312±0.02	0.23 ± 0.02	105 ± 1.6	97.5± 6.5	1.64± 0.24	1.94 ± 0.71

Film Thickness

Thickness of the developed formulations F1 to F9 varied from 0.17 ± 0.01 to 0.29 ± 0.04 mm and was found to be uniform.

The thickness increased with increase in RLPO and RSPO concentration. The SD values were less than 1 for all formulations, an indication of more uniform patches

Folding Endurance

For various formulations, the folding endurance varied from 97 ± 7 to 123 ± 2 and it was found to increase with the increase in the Eudragit proportion.

Drug content uniformity:

Good uniformity in drug content was observed in all transdermal patches as evidenced by Table No.9. The drug content is ranged from 94.6 to 99.03%. From the results obtained (i.e., lowest SD values), it was clear that there was proper distribution of Labetalol in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulations.

Percentage of Moisture Content

Moisture content of the developed formulations F1 to F9 varied from 1.15 ± 1.25 to 2.13 ± 1.42 % (Table 4). The formulations F1 which is having high moisture absorption was found to be 2.13%. The formulations F5 which is having less moisture absorption was found to be 1.15%.

The results revealed that the moisture content was found to increase with increasing concentration of lipophilic polymer (RLPO, RSPO). The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage.

Percentage of Moisture Uptake

Moisture uptake of the developed formulations F1 to F8 varied from 3.36 to 1.25%. The formulations F5 which is having high moisture content was found to be 3.36%. The formulations F7 which is having less moisture absorption was found to be 1.25%.

Based on results; an increasing of the lipophilic polymer concentration (RSPO), the moisture uptake was increases. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness.

In Vitro Drug Diffusion Studies

The drug release from transdermal patches is mostly controlled by the chemical properties of the drug, the nature of formulation and the physiological and physicochemical properties of the biological membrane. The

release profile of labetalol from transdermal patches showed that formulation F8 and F9 exhibits greatest percentage of release (63.315, 63.557%) (Fig. 2).

The releasing properties of F5, F4, F1 was found to decrease with the increase of the RSPO concentration. Depending on the concentration of RLPO, the release of the drug is substantially increased. To examine the drug release Kinetics and Mechanism the data were fitted to models representing zero, first order, Higuchi and Peppas model (Figures). According to Higuchi model, the 'n' value ($0.77 \leq n \geq 0.96$) indicates that the amount of released drug was by non-fickian diffusion.

Formulation F3 (Eudragit RSPO-0.120 RLPO-0.160) was found to be best among all batches of its consistent release rate for 12 hrs and the extent of drug release 94.20%.

Stability studies

After 3 months physicochemical parameters of formulation F3 was determined. Table 5 showed that there were no significant changes found in physicochemical parameters as well as in physical appearance after stability study (Fig. 7).

Table 5: Physicochemical properties of F3 After stability Studies.

Formulation code		**F3**	
Time (Days)		**30**	**60**
Folding endurance	A	111.66 ±7.6	112 ± 11.01
%Content uniformity	A	96.04 ± 0.15	94.19 ± 2.92
% Moisture content	A	1.99 ± 0.53	1.42 ± 0.91
% Moisture uptake	A	1.67 ± 0.47	1.47± 0.42

Where A: 40°C±2°C/75%±5% RH.*n = 2

Conclusion

In the present investigation an attempt has been made to optimize, to design a matrix type transdermal film of labetalol using EUDRAGIT RSPO and RLPO as polymers by solvent casting method in order improve the drug's bioavailability.

The drug used is the best studied for hypertension treatment. The labetalol film was successfully formulated, which prevents the frequency of administration for an improved patient compliance. From the experimental

results obtained, F3 formulation has been selected as the best formulation. The drug in-vitro diffusion study from the formulation was found to be controlled release. All the formulations evaluation parameters were found to be satisfactory.

The in-vitro release data were fitted to various kinetic models (zero order, first order, Higuchi model and peppas model). According to the kinetic data it was found that drug release follows zero order release (Fig 4.) by diffusion technique from the polymer. Stability study of the formulation F3 showed no significant changes in the physical appearance and physicochemical characteristics of the film. Based on the obtained results, we can conclude that the attempt of formulation and evaluation of the matrix type transdermal film of labetalol found to be successful in the drug release for a period of 24 hrs.

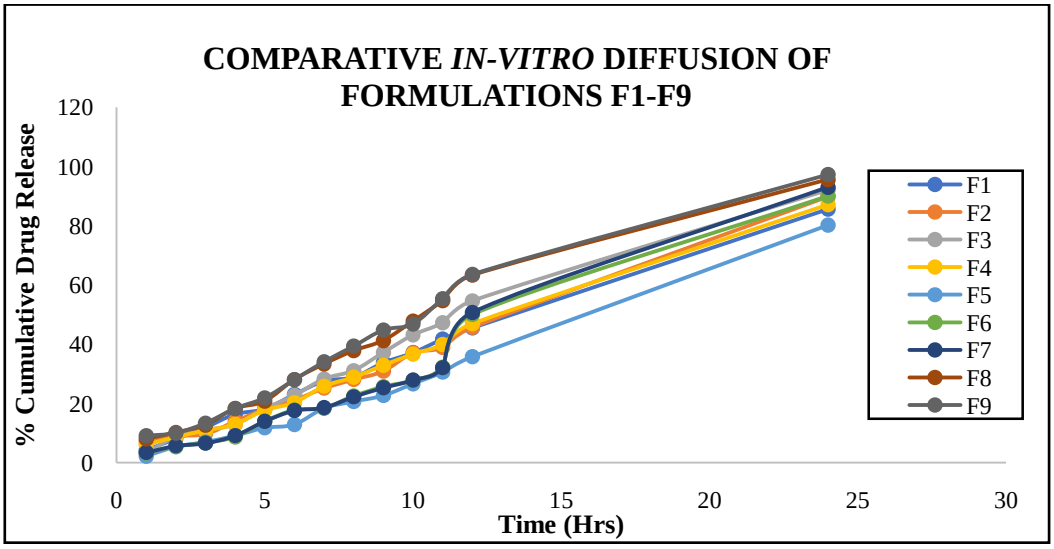

Fig. 3: Comparative *In-vitro* diffusion study of formulation F1-F9

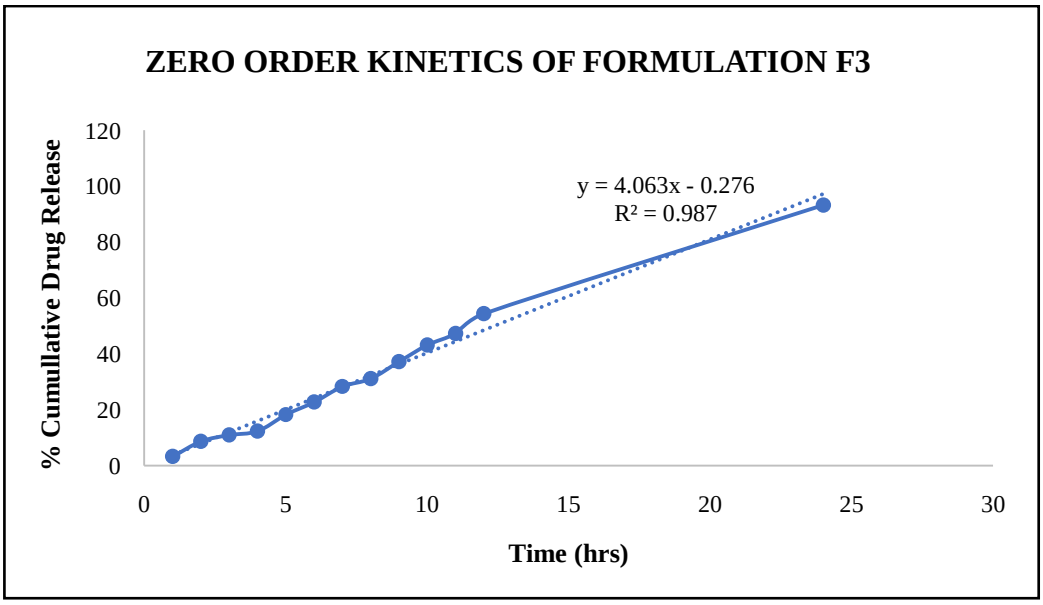

Fig. 4: Zero order kinetics of Formulation (F3)

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Corresponding Author:

Murhula Mongane Pascal*,

Email: murhulamongane@gmail.com