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TO OPTIMIZE THE EFFECT OF POLYMERS ON MATRIX TYPE TRANSDERMAL PATCH OF TRANDOLAPRIL

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Abstract: The present work based on Optimization of polymers on matrix type transdermal patch of Trandolapril. i.e. Eudragit NE30D and HPMC K15M were used to achieve a predetermined Sustain effect. Transdermal films were prepared using Eudragit NE30D (Hydrophobic polymer) and HPMC K15M (Hydrophilic polymer) and DMSO as a permeation enhancer at different concentrations. PEG 400 was incorporated as plasticizer respectively. A 3^2 full factorial design was employed to explore the effects of Eudragit NE30D and DMSO (independent variables) on folding endurance and % cumulative drug release at 24 hour. (Dependent variables). Further, the patches were also evaluated for uniformity of thickness and weight, surface pH, % drug content, folding endurance, % moisture absorbed, % moisture loss and *in vitro* drug diffusion. Results indicated that % cumulative drug release decreases with increasing the Eudragit NE30D and % cumulative drug release increased with increasing concentration of DMSO. Optimized formulation F3 showed satisfactory tensile strength, folding endurance and cumulative % drug diffusion at 24 hour of 796 ± 4.4, 324 ± 07 and 89.96 ±1.47 respectively. The selected formulation (F3) was found to be stable at 40 ± 0.5 °C and 75 ± 5% RH during the test period of 1 month. From the results, it can be concluded that transdermal patches for Trandolapril with desired characteristics could be prepared (polymer concentration Eudragit NE30D 7%, HPMC K15M 3%, PEG 400 30%w/w of dry polymer and DMSO 15 %w/w of dry polymer).

Keywords: Transdermal patch, Trandolapril, *In vitro* drug diffusion, Folding endurance

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INTRODUCTION

Transdermal Drug Delivery System adheres to the body surface and delivers the drug, across the skin at controlled rate in to the blood stream. Transdermal drug delivery system is self contained, discrete dosage form. Transdermal drug delivery system is also known as a transdermal patch or skin patch which deliver a specific dose of medication to the systemic circulation. It is a medicated adhesive patch. Transdermal drug delivery system is a Novel drug delivery system and its aim to achieve a programmed delivery of the therapeutic products when applied on the skin for the optimal beneficial effects while avoiding the side effect of drugs. Transdermal drug delivery system is topically administered medicaments. In the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication.

Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers.[4]

TRANSDERMAL PATCH[3,4-7]

A transdermal patch is also known by the name of skin patch which is used to deliver the specific amount of dose through skin and it directly goes into the blood stream. Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medicament in to the patient. A wide variety of drugs are delivered by transdermal patches. A new crystal reservoir technology has come out successfully with the advancement in TDDS which produce comparable smaller patches with a more controlled and sustained release.

Advantages of transdermal drug delivery system

- Eliminate hepatic first pass metabolism.
- Provide steady delivery.
- Increase compliance.
- Reduce systemic drug interaction.

- Permit dose discontinuation via removal.
- Improved bioavailability.
- Longer duration of action.
- More uniform plasma levels.
- Self administration is possible.
- Minimal inter and intra patient variation because the composition of skin structurally and biologically is the same in almost all the humans.
- Avoidance of gastrointestinal incompatibility.
- Avoidance of hazards and discomfort associated with parenteral therapy.
- Improves patient compliance, as it is easy to apply.
- Steady and optimum blood concentration time profile achieved.
- Release of drug for prolonged time with single application which extend the duration of activity.
- Elimination of typical multiple dosing.[5]

Trandolapril is an Angiotensin Converting Enzyme (ACE) inhibitor used to treat high blood pressure, used as an adjunct in the treatment of congestive heart failure (CHF). Trandolapril has short half life (4-6 hours) so frequent dosing of drug is required which is not good for patient compliance. Due to its high first pass metabolism it has low oral bioavailability(4-14%). To overcome this oral route problem, transdermal route is selected. Trandolapril has low dose size (2&4 mg) and low molecular weight makes it suitable candidate for administration by transdermal route. Transdermal route avoid first pass metabolism and reduce dose frequently and increase bioavailability.

MATERIALS AND METHODS

Trandolapil was obtained as a gift sample from Hetero healthcare Ltd. (Hyderabad). Eudragit NE30D, HPMC K15M, PEG 400, DMSO, was obtained as a gift sample from S. D. Fine Chemicals. All other chemicals used were of analytical grade.

Drug Excipient Compatibility Study

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm-1 by KBr disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and polymers and physical mixture of drug with all polymers. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug and polymers.

Preparation of trasdermal patch of Trandolapril.

The transdermal patch was optimized by using 3^2 full factorial design.(Table 1) In this study, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. The amounts of Eudragit NE30D (X1) and DMSO (X2) were selected as independent variables. These nine formulations were studied and optimized for Folding endurance and % cumulative drug release at 24 hour. The data was inte

Solvent casting method

Polymers Eudragit NE 30D (7%, 8%, 9%) and HPMC K15M (3%) were weighed accurately and dispersed with stirring in water. Trandolapril (72.34 mg) was weighed accurately and dissolved with stirring in methanol add varying amounts of DMSO (5%, 10%, 15%) The polymeric dispersion was added to drug solution with gentle stirring, followed by addition of PEG 400 (30%) to the solution. The solution was kept in a sonicator for 20 min. Then solution was poured into a clean and dry glass petri dish and allowed to dry. The dried films were carefully removed from the petri dish, checked for any imperfections or air bubbles and cut in to pieces of 4 cm^2.

Evaluation of Transdermal patch of Trandolapril

Thickness

The thickness of the patch was determined using a vernier calliper at three separate points of each patch. From each formulation, three randomly selected patches were tested for their thickness.[3]

Tensile Strength and % Elongation

A tensile strength of patch is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of iron. The 4 cm^2 patch equivalent to 2 mg drug from each formulation was taken. One end of the patch was sandwiched between the iron plates and fixed. Other end was connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the

hanging end of the thread. The force needed to fracture the patch was determined by measuring the total weight loaded in the pan. The weight corresponds to break the patches were taken as tensile strength.[3]

The following equation was used to calculate the tensile strength (TS)

Load*100/ Thickness*Width.

For determination of % elongation, the initial length of the patch was measured on scale and a pointer is attached to freely movable thread. Increase in length at the time of break of the patch was recorded and % elongation was calculated by following formula.

Initial length- Final length/ Initial length*100

Experiments were performed in triplicate and average value was reported.

Folding endurance

Folding endurance is determined by repeated folding of the patch at the same place till the strip breaks. The number of times the patch is folded without breaking is computed as the folding endurance value.[12]

Weight uniformity

The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.[3]

Drug Content

A specified area (4 cm2) of patch was dissolved in 10 ml phosphate buffer pH 7.4 and filtered through a filter medium. From that 1 ml taken and diluted upto 10ml. Then analyze the drug contain with the UV spectroscopy.[3]

% Moisture loss

The prepared patches are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches are to be reweighed and determine the percentage moisture content from the below mentioned formula.[5]

% moisture loss = [Initial weight- Final weight/ Final weight] ×100

% Moisture absorption

Weighed patches are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.[5]

% moisture absorption = [Final weight- Initial weight/ Initial weight]

Surface pH

Transdermal films were allowed to swell for 2 hr at 37 °C on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in worm isotonic phosphate buffer of pH 7.4 under stirring and then pouring the solution into a petri dish till gelling at room temperature. The surface pH was measured using pH meter by placing the electrode in contact with the surface of the swollen films and allowed to equilibrate for 1 min. The experiments were performed in triplicate and average pH of three determinations was Reported.[12]

***In vitro* diffusion study**

Goat skin was obtained from slaughter house. The skin was removed carefully and separated from the underlying cartilage with a scalpel. After separating the full thickness skin, the fat adhering to the dermis side was removed using a scalpel and isopropyl alcohol. The transdermal permeation was performed in modified Diffusion cell (surface area 3.14 cm2). While placing the patch, the donor compartment contains patch on stratum corneum side of skin and dermis side was facing receptor compartment. Receptor compartment contains phosphate buffer pH 7.4 and samples were withdrawn at regular time intervals and replaced the same with receptor fluid. The samples were analyzed at 224.4 nm against blank by UV spectrophotometer.[8 14]

Stability study

The stability study was carried out as per ICH guideline Q1C on the optimized formulation F3 based on evaluation parameters. The optimized formulations were sealed in aluminum packaging and kept in humidity chamber maintained 40 ± 2 °C / 75 ± 5 % RH for 1 month. At the end of study, samples were analyzed for the folding endurance, % drug content, % CDR and tensile strength.

RESULT AND DICCUSSION:

Drug Excipient Compatibility Study:

Infrared spectroscopy was used as means of studying drug-excipients interactions. It was found that there was no chemical interaction between Trandolapril and excipients used because there were no changes in the characteristic peaks of Trandolapril in the IR spectra of mixture of drug

and excipients as compared to IR spectra of pure drug.(Figure 1,2)

EVALUATION OF FACTORIAL DESIGN FORMULATIONS (F1 TO F9)

Thickness

Thickness of the various formulations (F1 to F9) are given in table 2 . Patches was in the range from 0.152 - 0.268 mm.

Tensile Strength

The results of tensile strength from various formulations (F1 to F9) are given in table 2. Tensile strength of all the patch was in the range of 725 ± 6.3 to 920 ± 5.7 gm/cm^2 suggesting all films were having good mechanical strengths to withstand mechanical damage during, production and application.

% Elongation

The results of % elongation from various formulations (F1 to F9) are given in table 2.The results revealed that % elongation was in the range of 13.24 ± 4.825 to 24.36 ± 4.542. This represents the elasticity of the patch. Increase in concentration of Eudragit NE30D results in enhancement of elasticity of patch.

Folding Endurance

The results of folding endurance of various formulations (F1 to F9) are given in table 2. All the patches were showing folding endurance in the range of 278 ± 08 to 324 ± 04. Results revealed that as the concentration of polymers increases folding endurance increases.

Drug content

The results of drug content of various films are given in table 3. The results indicate that drug content of films were in the range of 88.53 ± 1.84 to 92.73 ± 1.72%.

% moisture absorption

The results of % moisture absorption of various films are given in table 3. The results indicate that % moisture absorption of films were in the range of 4.220 ± 0.112 to 6.421 ± 0.152. From the result we conclude that as the concentration of polymer was increase there was increase in moisture absorption.

% moisture loss

The results of % moisture loss of various films are given in table 3. The results indicate that % moisture loss of films were in the range of 2.742±0.129 to 3.412±0.184. From the result we conclude that as the concentration of polymer was increase there was increase in moisture loss.

Surface pH:

The surface pH of prepared films was in the range of 6.44-6.82 with a very low value of standard deviation given in table 3. All the films were having surface pH close to skin pH suggesting that they will not irritate the skin.

Uniformity of weight:

The weight of prepared films was in the range of 0.153 to 0.196 mg given in table 3. In all the cases the calculated standard deviation values were very low which suggest that the prepared films were uniform in weight. The weight of the films increases as the concentration of polymer increases.

***In vitro* drug diffusion**

In vitro drug permeation profiles of Trandolapril from all prepared films are seen in table 4 and 5 & figure 3 and Figure 4. The results suggest that Eudragit NE30D and DMSO play an important role in the release of drug from the films. Films having higher concentration of Eudragit NE30D showed lower values of drug permeation as compared to films having lower amount of Eudragit NE30D Results of drug permeation showed that increased in DMSO concentration of % w/w of dry polymer increases the drug permeation significantly as shown in (Figure 3 and 4)

Stability study

The promising formulation F3 was subjected at 40 ± 0.5 °C temperature and 75 ± 5 % RH for 1 month to check the stability. The results of physical appearance, drug content, folding endurance and other parameters after 1 month storage of prepared transdermal patches are shown in (table 6 and 7)

CONCLUSION:

In the present investigation, factorial formulations F1-F9 were prepared using 7%, 8% and 9% of Eudragit NE30D and 5%, 10% and 15% (w/w of dry polymer) of DMSO (Dimethyl sulphoxide). HPMC K15M was incorporated as hydrophobic copolymer at concentration of 3%. The formulation F3 was selected as the promising formulation on the basis of tensile strength, % elongation, % drug content and mainly cumulative % drug diffusion. The cumulative % drug diffused of F3 was found to be 89.96 ±1.47. From the results stability study it can be concluded

that the films can be stored at 40 °C and 75% RH without any significant stability problems. The formulation satisfied all the pharmaceutical parameters of transdermal films and appears to be promising, would be able to offer benefits such as sustained drug release, reducing frequency of administration, improving bioavailability, and thereby may help to improve patient compliance.

Table 1. Formulation of transdermal patch of Trandolapril

Batch	Drug (mg)	Eudragit NE30D (%v/w)	HPMC K15M (%w/w)	PEG 400 (%w/w of dry polymer)	DMSO (%w/w of dry polymer)	Water: methanol
F1	72.34	7	3	30	5	7:3
F2	72.34	7	3	30	10	7:3
F3	72.34	7	3	30	15	7:3
F4	72.34	8	3	30	5	7:3
F5	72.34	8	3	30	10	7:3
F6	72.34	8	3	30	15	7:3
F7	72.34	9	3	30	5	7:3
F8	72.34	9	3	30	10	7:3
F9	72.34	9	3	30	15	7:3

Table 2. Evaluation parameter of transdermal patch of Trandolapril

Batch	Thickness (mm)*	Tensile strength (gm/ cm^2)*	% Elongation*	Folding endurance*
F1	0.123 ± 0.021	739 ± 2.4	19.25 ± 3.122	279 ± 11
F2	0.128 ± 0.011	725 ± 6.3	24.36 ± 4.542	301 ± 12
F3	0.199 ± 0.021	796 ± 4.4	21.27 ± 3.652	324 ± 07
F4	0.194 ± 0.022	793 ± 3.4	22.42 ± 4.545	278 ± 08
F5	0.205 ± 0.012	815 ± 5.6	18.13 ± 3.945	298 ± 06
F6	0.236 ± 0.030	846 ± 6.7	21.15 ± 4.335	312 ± 05
F7	0.251 ± 0.014	862 ± 3.4	14.32 ± 2.233	286 ± 04
F8	0.268 ± 0.021	903 ± 2.6	17.25 ± 3.452	306 ± 06
F9	0.249 ± 0.048	920 ± 5.7	13.24 ± 4.825	324 ± 04

Table 3. Evaluation parameter of transdermal patch of Trandolapril

Batch	% moisture absorption*	% moisture loss	Drug content (%)*	Surface pH*	Weight variation*
F1	4.220 ± 0.112	2.742 ± 0.129	88.53 ± 1.84	6.49 ± 0.354	0.158 ± 0.013
F2	4.284 ± 0.134	2.823 ± 0.153	91.32 ± 2.37	6.63 ± 0.137	0.153 ± 0.020
F3	4.851 ± 0.172	2.945 ± 0.109	92.21 ± 2.87	6.80 ± 0.153	0.169 ± 0.018
F4	4.835 ± 0.107	2.958 ± 0.122	92.73 ± 1.73	6.75 ± 0.314	0.163 ± 0.025
F5	5.254 ± 0.125	3.021 ± 0.108	91.42 ± 2.13	6.67 ± 0.325	0.172 ± 0.015
F6	5.562 ± 0.241	3.168 ± 0.145	89.14 ± 1.72	6.58 ± 0.249	0.179 ± 0.027
F7	6.126 ± 0.213	3.192 ± 0.164	91.46 ± 2.78	6.44 ± 0.254	0.190 ± 0.028

F8	6.293 ± 0.184	3.387 ± 0.173	89.25 ± 1.87	6.82 ± 0.363	0.194 ± 0.025
F9	6.421 ± 0.152	3.412 ± 0.184	90.32 ± 2.63	6.78 ± 0.168	0.196 ± 0.017

Table 4. *In vitro* drug release data of factorial formulations F1 to F5

Time (hr)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	13.93 ± 1.23	17.46 ±0.92	21.39 ±1.25	12.13 ±0.39	14.23 ±1.36
3	31.12 ±0.78	35.03 ±1.35	38.15 ±2.05	22.06 ±1.79	23.07 ±1.58
5	48.53 ±1.54	51.92 ±2.03	55.07 ±2.13	31.02 ±0.93	34.19 ±0.48
7	53.39 ±0.12	57.15 ±0.98	60.12 ±0.77	37.12 ±1.42	41.33 ±2.03
9	68.92 ±0.22	70.29 ±1.72	74.73 ±1.36	42.23 ±1.25	48.13 ±1.76
12	73.05 ±1.32	78.16 ±0.56	78.93 ±1.22	50.08 ±1.13	56.07 ±0.94
16	84.35 ±1.74	87.32 ±1.29	88.79 ±1.53	54.63 ±0.49	61.28 ±1.83
20	87.29 ±0.13	88.20 ±1.43	89.48 ±1.74	67.34 ±0.56	73.39 ±0.89
24	88.36 ±0.57	89.53 ±0.48	89.96 ±1.47	72.38 ±1.78	78.73 ±1.73

Table 5. *In vitro* drug release data of factorial formulations F6 to F9

Time (hr)	F6	F7	F8	F9
0	0	0	0	0
1	18.53 ±0.09	10.03 ±0.33	12.29 ±0.65	13.56 ±1.53
3	28.03 ± 1.12	21.62 ±0.65	22.41 ±1.30	26.32 ± 0.09
5	37.12 ±2.13	28.34 ±1.72	29.32 ±0.06	33.17 ±1.12
7	44.62 ±0.53	35.56 ±1.11	37.93 ±1.73	42.08 ±0.86
9	51.13 ±0.03	39.06 ±1.52	42.18 ±1.13	48.20 ±2.08
12	62.28 ±1.03	47.32 ±0.22	51.02 ±0.07	56.09 ±0.05
16	70.34 ±0.75	52.44 ±1.91	55.39 ±1.98	58.32 ±0.11

20	82.73 ±0.07	56.20 ±1.29	59.12 ±0.02	63.11 ±1.63
24	86.20 ±0.22	60.03 ±0.07	62.04 ±1.54	68.82 ±1.78

Table 6. Stability study of promising batch F3

Parameter	At 0 day	After 30 days
Thickness	0.199±0.021	0.197 ± 0.016
Tensile Strenght	796 ± 4.4	795 ± 2.3
% Elongation	21.27± 3.652	20.15 ± 1.562
Folding endurance	324± 07	321 ± 05
% Moisture Absorption	4.981± 0.172	5.022± 0.112
% Moisture Loss	2.945± 0.109	2.923 ± 0.220
Drug Content	92.21± 2.87	89.96 ± 1.23
Surface pH	6.80±0.153	6.72 ± 0.212
Weight Uniformity	0.169±0.018	0.167± 0.142

Table 7.

%Cumulative drug release study of F3 at 0 day and after 30 days

Time (min.) %Cumulative Release

	At 0 day	After 30 days
0	0.00 ± 0.000	0.00 ± 0.000
1	21.39 ± 1.25	20.48 ± 1.22
3	38.15 ± 2.05	36.22 ± 2.02
5	55.07 ± 2.13	52.21 ± 0.77
7	60.12 ± 0.77	58.36 ± 1.58
9	74.73 ± 1.36	71.33 ± 2.88
12	78.93 ± 1.22	75.56 ± 1.23
16	88.79 ± 1.53	81.73 ± 1.65
20	89.48 ± 1.74	85.14 ± 0.85
24	89.96 ± 1.47	88.92 ± 1.44

Figure: 1 FTIR spectra of Test sample

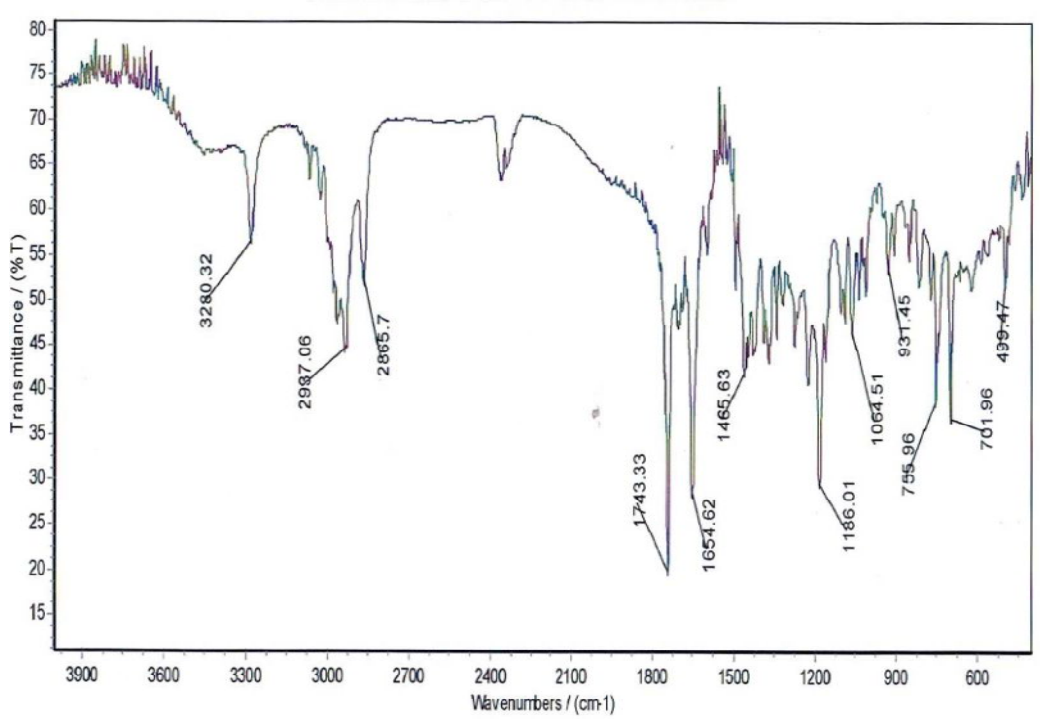


Figure: 2

FTIR spectra of Drug+Excipient

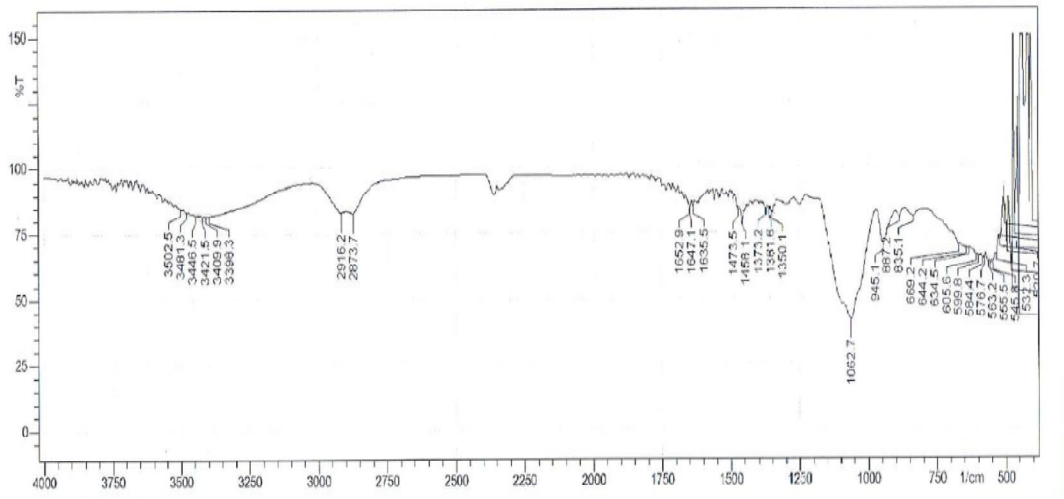


Figure: 3 *In vitro* Drug release of F1 to F9 batches

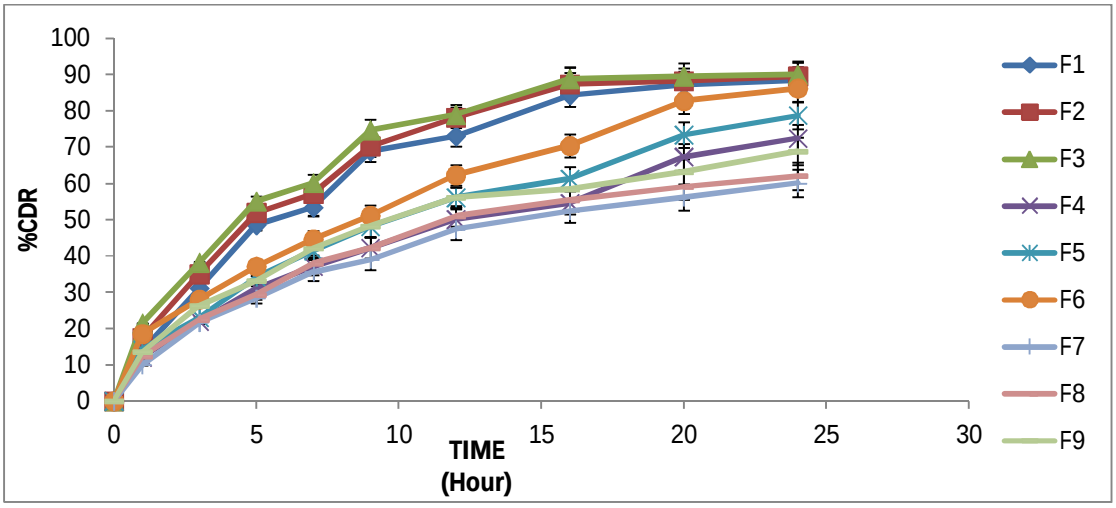
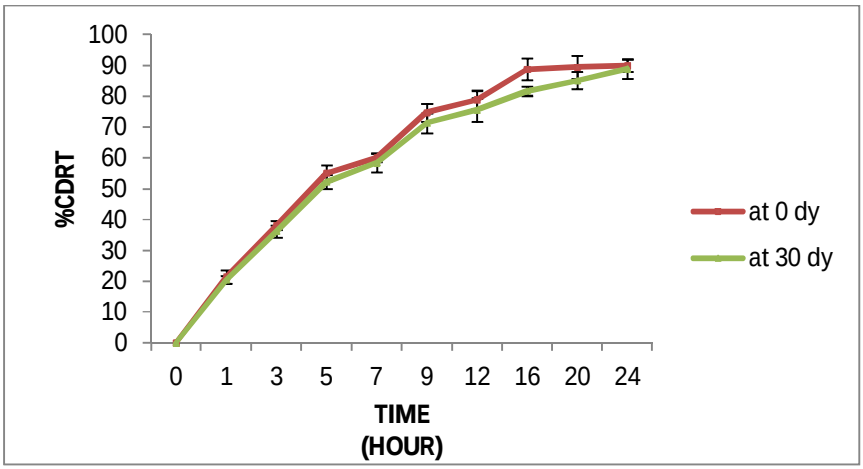


Figure: 4 *In vitro* Drug release of F1 to F9 batches after 30dys.



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