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FORMULATION, OPTIMIZATION & EVALUATION OF TRANSDERMAL PATCHES OF SALBUTAMOL SULPHATE

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ABSTRACT: Aim: The objective of the present research work was to formulate and compare two different kinds of penetration enhancer in transdermal patch with placebo patch using a drug (Salbutamol sulphate) and compare for *in vitro* drug release. **Study Design:** The transdermal patches of Salbutamol sulphate were prepared by solvent evaporation technique using different ratios of Hydroxy propyl methylcellulose (HPMC K15M) and Poly vinyl propylene (PVP K30). The prepared transdermal patches were evaluated on parameters like weight variation, thickness uniformity, moisture content, moisture uptake, folding endurance, tensile strength, drug content, *in vitro* dissolution studies, *in vitro* drug release, skin irritation test and stability studies. Maximum drug release was showed by Batch T, and the optimized formulation showed satisfactory characteristics.

INTRODUCTION: Transdermal drug delivery systems (TDDS) is type of drug delivery system designed to deliver a therapeutically effective amount of drug across a patient's skin. Typically, the Transdermal patches, stored in a pouch; at the time of use, the pouch is opened and patches applied to skin to releases the drug. The Transdermal patches, typically consists of a release liner (e.g. polyester), adhesive (e.g. polyisobutylene-based, acrylic, silicone-based), active pharmaceutical ingredient (i.e. drug), and backing (e.g. polyester). The system may also contain penetration enhancers, excipients, a rate-controlling membrane, and a protective film over the backing and over the release liner.

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Adhesive properties of patches can be affected by the type and concentration of additives used, thickness of the adhesive, type and concentration of permeation enhancers. Composition, thickness of the backing layer, residual solvent, type and concentration of the active pharmaceutical ingredient, give an impact on patch properties [1].

Transdermal route get advantage over conventional drug delivery system because it lowers the risk of toxicity or inefficacy in the case of drugs with narrow therapeutic window by providing the constant blood levels in plasma and also improves patient compliance by improving dosage regimens. In case of the drugs which have low bioavailability due to first-pass metabolism in the gastrointestinal tract and liver or short biological half-lives to be administered at most, once a day. The problems of the gastrointestinal environment, such as chemical degradation of the drug and gastric irritation, are avoided and drug input can be easily terminated by removing the patch from stratum corneum. Transdermal route is noninvasive alternative to

subcutaneous, parenteral and intramuscular injections and suitable for patients who are unconscious or vomiting. Along with these advantages there are some limitations of transdermal route as there is possibility of local irritation, erythema, itching at the site of application and heavy drugs molecules (>500 Daltons) usually difficult to penetrate the stratum cornea. Also drugs with very low or high partition coefficient fail to reach blood circulation through skin and the drug candidate must have some desirable physicochemical properties for penetration through stratum corneum.

MATERIALS AND METHOD:

Materials:

HPMC K15 M, PVP K30, Propylene glycol, Dimethyl sulphate (DMS) and Methanol were obtained from HiMedia Laboratories Pvt. Ltd., Mumbai. Salbutamol Sulphate and Tulsi oil was obtained from the lab of Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra.

Method of preparation of monolithic transdermal system:

The transdermal patches of pure Salbutamol sulphate drug were made by solvent evaporating technique using different ratios of HPMC K15 M [6% TO 10 %] and PVP K30. 5 mg of pure Salbutamol sulphate was weighed and dispersed in 10 ml distilled water [8]. Weighed amount of HPMC K15 M and PVP K30 was added to each aqueous drug solution with continuous stirring to ensure uniform distribution. Weighed amount of permeation enhancer is added to the solution. Propylene glycol was used to protect the polymeric patches from brittleness upon storage. The dispersion was done using a magnetic stirrer providing constant stirring (500 rpm) at room temperature until clear solution is obtained. Polymeric solution (10ml) was poured onto a prepared cavity (circular dish of 57 mm² diameter & 8 mm depth) and dried at room temperature for 72 hr with an inverted funnel overhead to provide a uniform rate of evaporation. Formulated patches were put in a desiccator over anhydrous calcium chloride for 24 hr before the evaluation process to assure total hydration and to eliminate entrapped air. The patches were evaluated within one week from the date of casting.

Qualitative and Quantitative Evaluation:

Transdermal Patches of all formulations were evaluated for uniformity of weight [2], thickness of the patch, moisture content**,** moisture uptake [3], tensile strength [3], drug content [4], folding endurance and flatness.

In vitro dissolution studies:

The *in vitro* dissolution test was practiced using USP type 1 test apparatus. The drug release study was carried out for 9 hr in 900 ml of phosphate buffer pH 6.8 dissolution media, maintained at 37±0.5ºC and agitated at 50 rpm. Periodically 5 ml sample was withdrawn at regular intervals and filtered through filter paper and samples were replaced by its equivalent volume of dissolution media. The samples withdrawn were assayed spectrophotometrically at 263 nm using shimazdu spectrophotometer. The percentage cumulative drug release was figure out and amount of salbutamol sulphate released from patches was determined [5].

In vitro permeation studies:

In vitro **diffusion studies:** The diffusion cell consists of two chambers, the receptor and the donor. The donor compartment is open at the top. The receptor compartment is enclosed by a water jacket for maintaining the temperature at 37±5ºC and is provided with a sampling port. The cellophane membrane containing patch was mounted between donor and receptor compartment. Phosphate buffer of pH 7.4 act as diffusion medium stirred with magnetic bead (operated by a magnetic stirrer) to prevent the formation of concentrated drug solution just below the membrane. Samples from the receptor compartment were taken at various time intervals over a period of 24 hr and the concentration of the drug was determined by UV spectrophotometer method using the standard curve. The amount of drug diffused at various time intervals was calculated and plotted against time [6].

Skin irritation Test:

The skin irritation test for drug was done on healthy rat weighing in between 150-200 g. The optimized transdermal patch formulation was evaluated for skin irritation studies on 12 rats (in two groups and each group having 6 rats). Dorsal portion hair removed physically with the help of

sharp scissors and the skin was washed properly one day before use. Group one was supplied with medicated formulation and group second were supplied with control formulation. Patches with drug was secured on experimental side by using an adhesive tape and non-medicated patch to control side of rats. The patches were removed after 72 hours and each of the area was observed for any sign of erythema or edema [5, 6].

Release kinetics: [7]

To interpret the mechanism and kinetics of drug release, the result outcome of *in vitro* drug release study were applied with different kinetic equations like zero order (% drug release vs. time), first order (log % unreleased drug vs. time), and Higuchi matrix (% drug release vs. square root of time). Drug release data was further analysed by Peppas equation, $Mt/M\infty=ktn$, where Mt is the amount of drug released at time t and $M\infty$ is the amount released at time ∞, the $Mt/M\infty$ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent, a measure of the primary mechanism of drug release to define a model which will represent a better fit for the formulation. Regression co- efficient (r^2) values were calculated for the linear curves obtained by regression analysis of the above plots.

Stability studies:

To provide the evidence on the quality of a drug substance which changes with time under the effect of variety of environmental factor such as temperature, humidity and light accelerated stability studies was performed. The optimized formulation was sealed in an aluminium foil and stored at 30±2ºC, RH 65±5% for 2 month as per ICH guidelines. Patches were periodically removed and evaluated [5].

RESULTS AND DISCUSSION:

The prepared transdermal patches and is quality control tests as per Indian Pharmacopoeia reveal that all the patches are meeting the official pharmacopeial requirements.

1. Uniformity of weight:

Medicated patches were tested for uniformity of weight and found uniform and were in the range of 150±2.53 to 172±1.98 mg.

2. Thickness of patch:

All the patches have uniform thickness throughout. The thickness was found in range of 0.325±0.017 to 0.395±0.021 mm.

3. Moisture Content:

The moisture content in all the formulations was found to be low and ranged from 2.6±3.21 to 7.2±1.04 (F-batch), 2.9±0.045 to 8.2±0.024 (D-batch), 3.1±0.019 to 8.1±0.021 (T-batch). The result revealed that the moisture content was increases with increasing concentration of hydrophilic polymers.

4. Moisture Uptake:

The moisture absorption in all the formulations was found to be low and ranged from 5.2±5.10 to 6.5±0.011%. The result revealed that the moisture absorption was found to increase with increasing concentration of hydrophilic polymers.

5. Folding Endurance:

Folding endurance of D6 was (253±2.01) and lowest of F1 (221±4.04).

6. Tensile Strength:

The tensile strength of the patches varies with concentration of polymer as the concentration increases tensile strength increases. It was found between 0.53±0.09 to 0.98±0.14 kg/cm^2. The formulation T5 shows higher tensile strength.

7. Drug Content Determination:

The drug content varied between 97.02±0.88 to 99.00±0.54%

8. *In vitro* drug release study:

Among the formulations F1-F9, F5 (HPMC: PVP in 1.4:1) showed percentage release at 52.85±0.056, 69.28±0.341 and 84.28 ±0.034180, 360 and 540 min. respectively. From formulations D1-D9, D5 (HPMC: PVP in 1.4:1 and DMSO 8%) showed percentage release 58.57±0.034, 74.28 ±0.033 and 87.85 ±0.033 at 180, 360 and 540 min. respectively. From formulations T1-T9, T5 (HPMC: PVP in 1.4:1 and Tulsi oil 8%) showed percentage release 62.14 ±0.093, 80.71 ±0.033 and 92.14±0.089 at 180, 360 and 540 mins respectively. Further, by comparing above formulations it was concluded that T5 showed best release as compared

to D5 and F5. In the present study it was observed that as the concentrations of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially also with increase in penetration enhancer concentration.

9. *In vitro* drug permeation study:

Among the formulations F1-F9, F5 (HPMC: PVP in 1.4:1) showed percentage release of 52.85±0.056, 69.28±0.341 and 84.28±0.034 at 180, 360 and 540 min. respectively. From formulations D1-D9, D5 (HPMC: PVP in 1.4:1 and DMSO 8%) showed percentage release 58.57±0.034, 74.28 ±0.033 and 87.85 ±0.033 at 180, 360 and 540 min. respectively. From formulations T1-T9, T5 (HPMC: PVP in 1.4:1 and Tulsi oil 8%) showed percentage release 62.14 ±0.093, 80.71 ±0.033 and 92.14±0.089 at 180, 360 and 540 mins respectively. Further, by comparing above formulations it was concluded that T5 showed best release as compared to D5 and F5. In the present study it was observed that as the concentrations of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased considerably also with increase in penetration enhancer concentration.

The cumulative percent of drug permeated from the patch F1-F9, F5 (HPMC: PVP in 1.4:1) showed percentage penetrate 26.66±0.018, 46.85±0.034 and 72.50±0.052 at 180, 360 and 1440 min. respectively. From formulations D1-D9, D5 (HPMC: PVP in 1.4:1 and DMSO 8%) showed percentage penetrate and 36.44±0.081, 63.61±0.051 and 93.20±0.085 at 180, 360 and 1440 min. respectively. From formulations T1-T9, T5 (HPMC: PVP in 1.4:1 and Tulsi oil 8%) showed percentage release 38.85±0.093, 66.15±0.089 and 97.90±0.034 at 180, 360 and 1440 min. respectively. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix and also with concentration of penetration enhancer. The highest percentage cumulative drug permeated was found in formulation T5 PVP and HPMC in the ratio of 1: 1.4 and penetration enhancer i.e. Tulsi oil of 8%. From perusal to above all data it was concluded that tulsi oil shows maximum release as compared with DMSO and formulations without penetration enhancer.

Rate of release was higher in patches containing high conc. of HPMC and penetration enhancer, it may involve a faster mode of diffusion of drug from the formulation.

Batch F5(93.20±0.085%) and Batch T5 (97.90±0.034%) showed highest cumulative drug permeated. So optimization studies were carried out on batches having penetration enhancer DMSO and tulsi oil and compared which one showed best results.

Release mechanism of optimized formulation:

Optimization was done from software Design Expert version 9.0. The regression value for the optimized batch is higher with 1st order and therefore the release kinetics followed 1st order. R^2 value is higher for First order and Higuchi. Hence, Salbutamol sulphate release from optimized batch followed is concentration and time dependent and penetration of drug from patches was governed by diffusion mechanism.

TABLE 1: COMPOSITION OF TRANSDERMAL PATCHES

Sr. No	HPMC(mg)	PVP K30 (mg)	Conc. of Propylene Glycol	Solvent (water: methanol)	Conc. of Permeation Enhancer(ml) F(Batch)	D(Batch)T(Batch)	
1	300	500	10%	4:1	-	4	4
2	500	500	10%	4:1	-	4	4
3	700	500	10%	4:1	-	4	4
4	300	500	10%	4:1	-	6	6
5	500	500	10%	4:1	-	6	6
6	700	500	10%	4:1	-	6	6
7	300	500	10%	4:1	-	8	8
8	500	500	10%	4:1	-	8	8
9	700	500	10%	4:1	-	8	8

TABLE 2: CHARACTERIZATION OF TRANSDERMAL PATCHES OF SALBUTAMOL SULPHATE BATCH -F

Sr No	Batch Code	Weight Variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content (w/w) (%)	Moisture uptake (w/w) (%)	Tensile strength (kg/cm^2)
1	F1	150±2.53	0.325±0.017	221±4.04	97.02±0.88	2.6±3.21	3.3±1.04	0.53±0.09
2	F2	161±2.90	0.328±0.023	243±4.01	97.74±5.02	5.5±2.31	4.2±1.19	0.84±0.07
3	F3	152±1.11	0.390±0.012	220±3.11	97.42±2.04	3.1±1.90	3.0±2.03	0.58±0.12
4	F4	158±1.42	0.352±0.011	250±2.13	97.62±2.50	4.1±1.05	4.3±3.11	0.63±0.14
5	F5	160±2.05	0.367±0.017	222±1.22	97.95±3.01	7.2±1.04	5.2±5.10	0.95±0.01
6	F6	155±1.50	0.346±0.011	243±5.11	97.12±0.87	3.3±2.01	3.1±3.12	0.57±0.12
7	F7	165±1.66	0.387±0.013	247±2.12	97.78±1.07	6.1±2.21	4.7±2.10	0.86±0.12
8	F8	158±1.41	0.395±0.021	238±2.12	97.57±1.76	4.6±1.90	4.4±1.01	0.68±0.03
9	F9	156±1.51	0.383±0.012	227±1.33	97.64±2.33	5.0±2.00	4.4±0.99	0.70±0.09

TABLE 3: CHARACTERIZATION OF TRANSDERMAL PATCHES OF SALBUTAMOL SULPHATE BATCH-D

Sr No	Batch Code	Weight Variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content (w/w) (%)	Moisture uptake (w/w) (%)	Tensile strength (kg/cm^2)
1	D1	161±1.45	0.374±0.019	244±5.06	98.25±0.72	6.2±0.031	4.0±0.021	0.60±0.18
2	D2	164±1.34	0.366±0.014	237±4.07	98.85±0.98	3.5±0.019	3.2±0.014	0.92±0.09
3	D3	163±1.43	0.378±0.019	244±3.01	98.15±1.09	4.4±0.056	4.8±0.017	0.55±.019
4	D4	167±1.32	0.368±0.017	232±3.09	98.53±0.88	2.9±0.045	3.4±0.09	0.64±0.07
5	D5	172±1.33	0.364±0.028	248±2.22	98.96±0.57	8.2±0.024	6.5±0.011	0.88±0.19
6	D6	164±1.47	0.349±0.016	253±2.01	98.21±0.70	4.3±0.032	3.7±0.012	0.57±0.11
7	D7	170±1.54	0.390±0.028	243±3.10	98.76±1.03	6.1±0.021	4.8±0.019	0.96±0.13
8	D8	167±1.33	0.367±0.018	225±4.19	98.56±0.98	4.7±0.023	3.4±0.024	0.65±0.18
9	D9	168±1.43	0.346±0.016	251±3.18	98.46±0.87	5.6±0.014	4.5±0.034	0.66±0.08

TABLE 4: CHARACTERIZATION OF TRANSDERMAL PATCHES OF SALBUTAMOL SULPHATE BATCH –T

Sr No	Batch Code	Weight Variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content (w/w) (%)	Moisture uptake (w/w) (%)	Tensile strength (kg/cm^2)
1	T1	168±1.98	0.395±0.067	225±4.07	98.17±0.99	3.7±0.032	3.2±0.045	0.56±0.06
2	T2	162±1.78	0.375±0.056	242±4.49	98.67±0.56	5.6±0.012	4.7±0.056	0.96±0.01
3	T3	160±1.97	0.374±0.032	245±3.87	98.45±0.76	3.1±0.019	3.6±0.023	0.58±0.12
4	T4	166±2.03	0.353±0.019	249±2.98	98.35±0.87	4.4±0.023	4.1±0.012	0.64±0.02
5	T5	172±1.98	0.374±0.031	239±3.42	99.00±0.54	8.1±0.021	5.3±0.015	0.98±0.14
6	T6	163±2.16	0.342±0.021	243±4.01	98.54±0.56	3.6±0.045	3.3±0.018	0.57±0.09
7	T7	171±1.76	0.384±0.023	247±3.09	98.75±0.65	6.6±0.034	4.9±0.019	0.91±0.14
8	T8	168±1.55	0.382±0.015	252±2.76	98.18±0.62	4.9±0.032	4.3±0.031	0.70±0.08
9	T9	169±1.98	0.368±0.014	246±2.91	98.20±0.44	5.5±0.025	4.4±0.023	0.72±0.14

TABLE 5:

Time(min)	%CDR F5	%CDR D5	%CDR T5
30	10.15±0.023	16.38±0.042	20.44±0.032
60	17.14±0.042	24.00±0.062	29.33±0.073
120	23.23±0.065	27.04±0.078	34.03±0.028
180	26.66±0.018	36.44±0.081	38.85±0.093
240	36.19±0.032	47.74±0.063	52.06±0.063
300	40.25±0.026	53.20±0.056	58.03±0.072
360	46.85±0.034	62.98±0.066	68.69±0.095
420	53.20±0.059	75.93±0.024	78.34±0.044
480	61.84±0.073	81.65±0.031	85.07±0.082
540	72.50±0.052	93.20±0.085	97.90±0.034

TABLE 6: RELEASE MECHANISM OF OPTIMIZED FORMULATION [9, 10]:

Formulation Code	R^2			
	Zero order	First order	Higuchi Model	Korsmayer Peppas model
Batch T5	0.916	0.99	0.976	0.967

TABLE 7: CHARACTERIZATION OF OPTIMIZED BATCH AFTER STABILITY STUDIES

Batch Code	Weight Variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content (w/w) (%)	Moisture uptake (w/w) (%)	Tensile strength (kg/cm^2)	Flatness (%)
T5	170±0.045	0.370±0.034	232±3.98	98.75±0.034	7.5±0.023	4.5±0.019	0.95±0.12	100.01

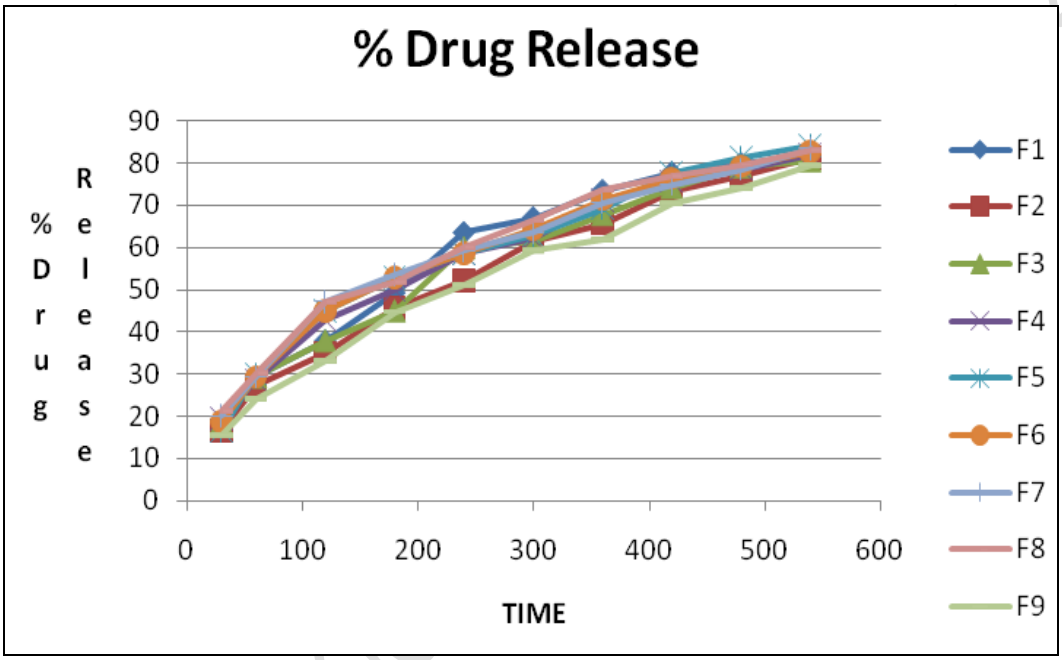

FIG. 1: *IN-VITRO* DRUG RELEASE PROFILE OF BATCH F

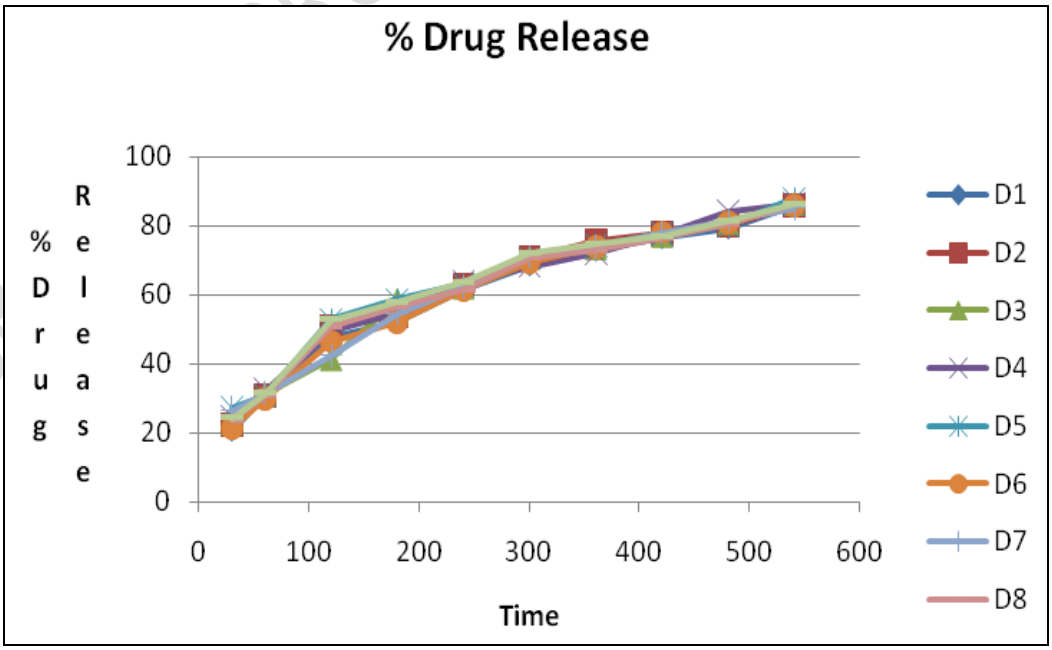

FIG. 2: *IN-VITRO* DRUG RELEASE PROFILE OF BATCH D

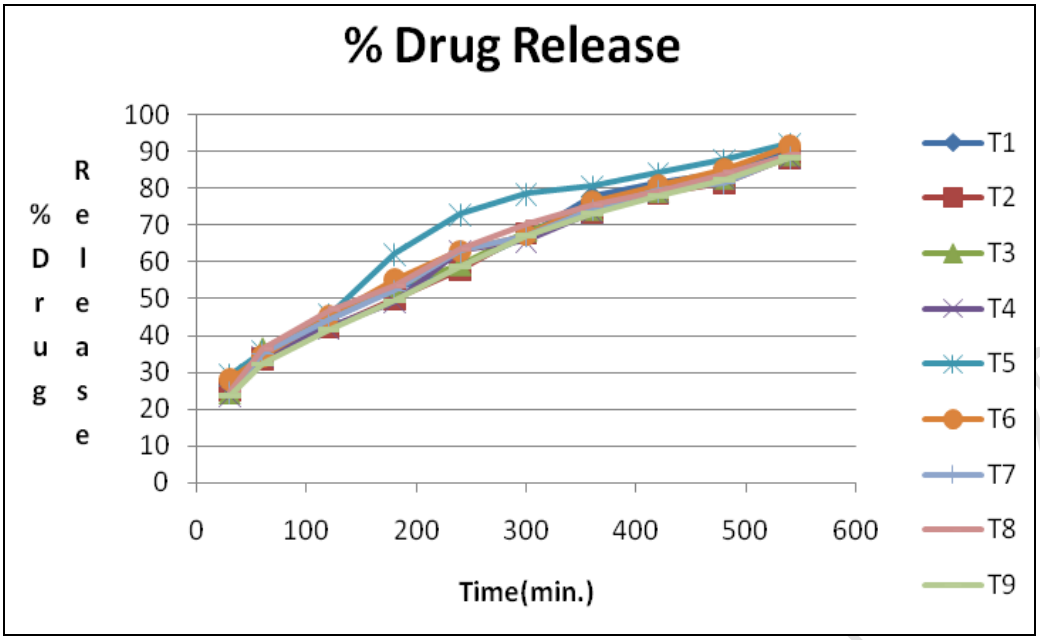

FIG. 3: *IN-VITRO* DRUG RELEASE PROFILE OF BATCH T

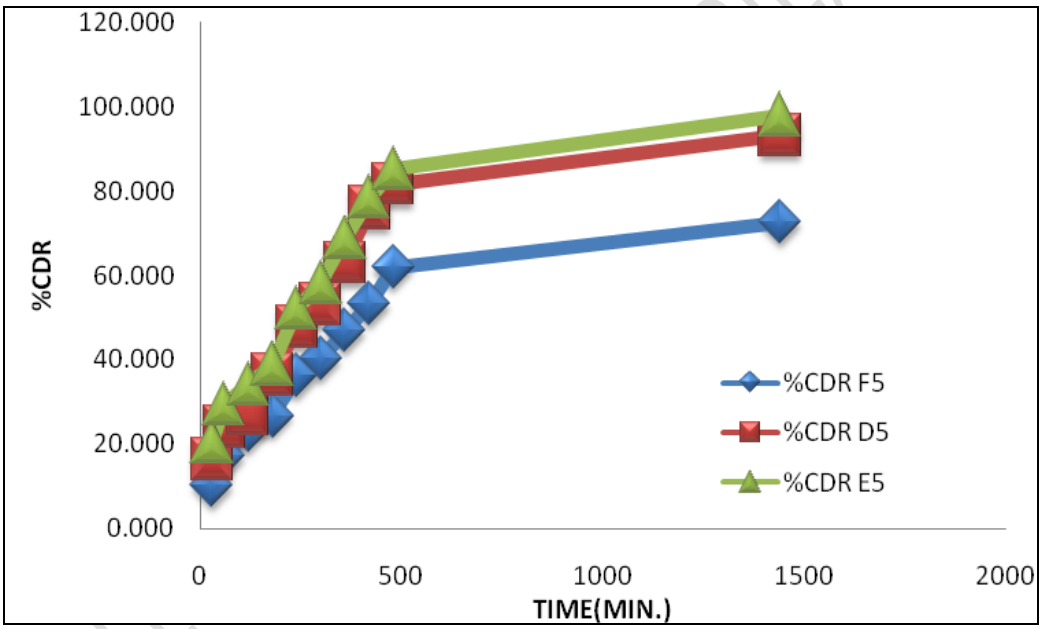

FIG. 4: GRAPHICAL REPRESENTATION OF *IN VITRO* DRUG PERMEATION WITHOUT PENETRATION ENHANCER, SYNTHETIC AND NATURAL PENETRATION ENHANCER OF FORMULATION 5, ONE MORE ERROR IN FIGURE WRITE BATCH T5 IN PLACE OF E5

Summary:

The *in vitro* drug permeation data of salbutamol sulphate across cellophane membrane showed that as the concentration of hydrophilic polymer and penetration enhancer (DMSO and tulsi oil) increases the permeation rate increased significantly as compared to formulations without any penetration enhancer. From relative graphs of patches without penetration enhancer, DMSO and tulsi oil patches it was concluded that patches with tulsi oil (Formulation T5, 6% w/w) showed higher permeation across membrane i.e 97.90±0.034% than DMSO (Formulation D5, 6%) i.e 93.20±0.085%. It was also concluded that as the concentration of polymer (HPMC) and penetration enhancer increased in the formulation, the drug release rate increase substantially as compared to formulations without penetration enhancer. Batch F i.e without permeation enhancer showed poor release, where as in Batch D, D5 showed maximum release 87.85% which was higher than F Batch but lesser than T Batch showed 92.14% drug release.

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