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Formulation and evaluation of transdermal patch of carbamazepine

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Abstract

Transdermal drug delivery system (TDDS) is a widely accepted mode of drug delivery method due to various advantages and one of the novel routes for systemic delivery of drugs through intact skin. Topical drug administration is a systemic and localized method of delivering drugs through skin and is considered an attractive alternative to oral and parenteral routes. The aim of present study was to formulate and evaluate Matrix type transdermal drug delivery system (TDDS) of Carbamazepine was prepared by the solvent evaporation technique. Several batches were prepared by using combination of HPMC E-15, Eudragit RL-100, and Ethyl Cellulose different ratios. Propylene glycol was used as plasticizer and DMSO was incorporated as a permeation enhancer. These Formulated transdermal patches were characterized for their physicochemical parameters like thickness, weight variation, folding endurance, percentage moisture uptake, Percentage moisture uptake and In vitro drug release studies were examined. Among the above all formulation F6 was chosen as a best Formulation, because this optimised formulation showed satisfactory drug content, physical characteristic for its thickness, weight uniformity, percentage moisture content, percentage moisture uptake, and maximum % of drug release i.e., 93.95 % in 12 hours. The optimized formulation (F6) showed maximum highest percentage of drug release.

Keywords: Carbamazepine; TDDS Patch; Hydrophilic Polymers; Hydrophobic polymer; Plasticizers; Permeation enhancer

1. Introduction

The novel drug delivery system is the side specific drug delivery system. It is new approach of pharmaceuticals by the using of this technique, in this technique the micron size particle is used for the drug carrier for the drugs the drug is inserted in the polymers and dendrimer and then it injected in the body and give the specific action New drug delivery system development is largely based on promoting the therapeutic effects of a drug and minimizing its toxic effects by increasing the amount and persistence of a drug in the vicinity of a target cell and reducing the drug exposure of non-target cell.

Transdermal drug delivery (TDD) has been extensively researched in recent decades due to advantages such as enhanced patient compliance, better drug release, and tissue targeting, among others (Carter et al., 2019). TDD could replace a number of methods, including some oral delivery of drugs, hypodermic injection and even some vaccines (Dong, 2016; Glenn & Kennedy, 2006). With better technology and knowledge about TDD systems, the treatment of various conditions could be made easier both for the health care system and the patients.

1.1. Advantages of TDDS

This route offers various therapeutic benefits over other drug delivery systems, as mentioned below.

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- Maintains constant level of the drug in the plasma, for drugs having shorter biological half lives.
- Reduces the dosing schedule.
- Avoids first-pass metabolism of the drugs having poor oral bioavailability.
- Improves patient compliance.

1.2. Disadvantages of TDDS

- The transdermal route of administration is unsuitable for drugs that irritate or sensitize the skin.
- Only relatively potent drugs are suitable candidates for transdermal delivery due to the natural limits of drug entry imposed by the skins impermeability.
- Technical difficulties are associated with the adhesion of the systems to different skin types and under various environmental conditions as well as the development of rate-controlling drug delivery features.

The factors influencing the suitability of drugs for transdermal delivery using current technology are as follows.

- The daily systemic dosage must be below 20 mg.
- The molecular size of drug must be below 500 Da.
- The log P (lipophilicity) of drug should be in the range 1-3.
- The melting point of drug should be below 200 ^{0}C.
- The drug should not irritate the skin.
- The drug should not bring about immune response in the skin.

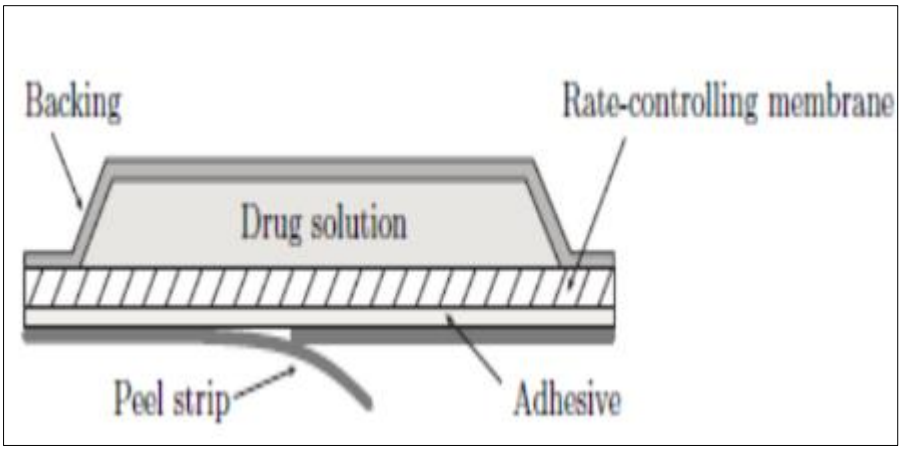

Figure 1 Matrix -based transdermal patch

1.3. Types of Transdermal Patches

Commercially available TDDS can be categorized as (i) reservoir systems, (ii) matrix systems without a rate-controlling membrane and (iii) matrix systems with a rate controlling membrane. Reservoir systems consist of three major components: the drug reservoir, the rate-controlling membrane and the adhesive. Typically, the drug reservoir contains the drug and excipients.

Main Components of Transdermal Patches.

- Liner - Protects the patch during storage. The liner is removed prior to use.
- Drug - Drug solution in direct contact with release liner
- Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin
- Membrane - Controls the release of the drug from the reservoir and multi-layer patches
- Backing - Protects the patch from the outer environment.

1.4. Polymers Used in Transdermal Patches

Polymers are the backbone of TDDS. Advances in the field of polymer science have paved the way for TDDS designs that have considerable flexibility.

Polymers play a key role in human body. Polymers are classified into three types: Natural, semisynthetic, and synthetic. Selection of polymer is very important for the development of product. And also polymers having several ideal properties, these properties are playing a major role in this system. Ideal properties such as

- It should be chemically inert.
- It should be nontoxic.
- It doesn't decompose during storage.
- Diffusion of drug is depended on the chemical, physical character of polymer and also depend molecular weight of polymer.

Polymers are used in TDDS in various ways, including as

- Matrix formers.
- Rate-controlling membranes.
- Pressure sensitive adhesives. (psa)
- Backing layers.
- Release liners.

1.5. Various Methods For Preparation TDDS

- 1) Asymmetric TPX membrane method, 2) Circular teflonmould method,
- 3) Mercury substrate method, 4) by using "IPM membranes" method,
- 5) By using "EVAC membranes" method, 6) Aluminium backed adhesive film method.

1.6. Anticonvulsants

Anticonvulsants (antiepileptics or AEDs) helps to normalise the way nerve impulses travel along the nerve cells which helps prevent or treat seizures. When the brain is working normally the nerve cells talk to each other using controlled electrical signals from one nerve cell to another. This tells the body to do everything it needs or wants to do.

Anticonvulsants stabilize the level of nerve cell impulses and are used for a range of conditions including

- Epilepsy
- Seizure disorders
- Nerve pain (neuropathic pain)
- Bipolar disorder.

Carbamazepine (5H-dibenzo-[b,f]-azepine-5-carboxamide: Tegretol - CBZ) was discovered by the chemist Walter Schindler of Switzerland in 1953. Carbamazepine is an iminostilbene derivative that is structurally related to the tri-cyclic antidepressants and contains the dibenzazepine ring system of the psychotherapeutic drug, imipramineCBZ is known as5 carbamyl-5H-dibenzo[b,f]azepine [1,5], 5H-dibenzo[b,f]azepine-5- carboxamide [1,4,9, 10, 11), CBZ is a tricyclic anticonvulsant that is primarily used for the treatment of partial and secondary generalised seizures in epilepsy (Marson et al. 2007). Carbamazepine is the "first line" AED prescribed for the treatment of epilepsy and several neurological disorders in humans.

2. Materials and methods

2.1. Materials

Carbamazepine was purchased from Yarrow chemicals, Mumbai. Polymers such as Hydroxy propyl methyl cellulose E15, Eudragit RL100, Ethyl Cellulose and other chemicals such as propylene glycol and DMSO and methanol provided by the institute (St John's College of pharmaceutical sciences) used in the study were of analytical grade.

2.2. Formulation Design of Transdermal Patch

Patches were prepared by Solvent Evaporation Method.

- Step 1- Required quantity of polymer was weighed and it was sprinkled slowly on surface of purified water for 2 hrs. After which it was continuously stirred by mechanical stirrer, till the polymer soaked in the water.

- Step 2- With continuous stirring. Now the appropriate quantity Propylene glycol, DMSO was added , which behaves as the penetration enhancer, followed by the required quantity .
- Step 3- Finally the drug was added with continuous stirring till drug get dispersed in completely.

Table 1 Quantitative Composition of Carbamazepine TDDS Formulation

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Carbamazepine (mg)	150	150	150	150	150	150	150	150	150
Hydroxy propyl methyl cellulose E15 (mg)	75	150	250	-	-	-	-	-	-
Eudragit RL100 (mg)	-	-	-	75	150	250	-	-	-
Ethyl Cellulose(mg)	-	-	-	-	-	-	75	150	250
Propylene glycol(ml)	1	1	1	1	1	1	1	1	1
Dimethyl Sulfoxide (DMSO) (mg)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Dicholoromethane : Methanol (ml)	5	5	5	5	5	5	5	5	5
Methanol(ml)	10	10	10	0	10	10	10	10	10

2.3. Formulation of Carbamazepine matrix patch:

The matrix transdermal Patch containing Carbamazepine was prepared by solvent casting technique. Nine formulations were formulated using different ratios of polymers and plasticizer. Polymer and drug was accurately weight. Then firstly, the polymer was dissolved in the solvent and mix was for up to 10-15 minutes, then the required drug was added to the polymer solution and mix thoroughly with vortex shaker, to the mixture solution plasticizer (Propylene Glycol) and penetration enhancer (DMSO) were added and vortexed more for homogenous mixture. Then it was poured in the Petri dish which was previously lined with aluminium foil and dried at 60 ^{0}C for 20 minutes in the hot oven. The dried patches were cut into small patches of 1 cm^2 and stored at desiccators for further study.

2.4. Experimental section

2.4.1. Preformulation studies

Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical and analytical investigation in support of promising experimental formulations. Successful formulations take into account a drug's interactions with the physicochemical properties of other ingredients and their interactions with each other to produce a safe, stable, beneficial and marketable product.

2.4.2. Ultraviolet-visible spectroscopy

Calibration of standard curve of Carbamazepine

100 mg of Carbamazepine was accurately weighed and dissolved in 100 ml of phosphate buffer solution (PBS), pH 7.4 in 100 ml of volumetric flask. The resulting solution had a concentration of 1 mg/ml (1000 µg/ml). From the prepared stock solution, 10 ml was further diluted to make up to 100 ml using PBS, pH 7.4 with concentration of 100 µg/ml. Different aliquots of 1 ml, 2 ml, 3 ml, 4 ml, 5 ml were diluted up to 10 ml with buffer to give concentrations in the range of 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml and 50 µg/ml respectively. The absorbance of each solution was measured by UV-Visible spectrophotometer at 284 nm using PBS, pH 6.8 as blank. The graph of concentration versus absorbance was plotted.

2.4.3. IR Spectral Studies

KBr pellet technique was followed for this study. In this the sample and the KBr were taken in 1:300 ratio. The mixture of sample and KBr was triturated to make fine powder. The fine powder was made into pellets by using pellitizer. The transparent pellets were placed in the Perkin elmer FT-IR spectrometer and the spectrum was recorded. The FT-IR analysis was done for Carbamazepine and also for prepared formulations. The frequencies of the possible peaks of FT-IR spectra of Carbamazepine should match with the drug - excipients spectra. (Singh et al., 1993).

2.5. Evaluation parameters

2.5.1. Appearance/clarity

The transdermal patch formulations were observed carefully by naked eye for appearance/clarity, colour, flexibility, and smoothness presence of suspended particulate matter if any. It was further assessed by observing them against a dark and white background. (Jan et al., 2020).

2.5.2. Weight variation

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight. (Hull MS et al 2002).

2.5.3. Thickness

The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film. The thickness of the patches was determined by vernier calibre at different places and mean values are calculated and noted.

2.5.4. Folding endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. A patch on specific area was cut evenly and repeatedly folded at the same place until it was broken. Number of times the film could be folded at the same place without breaking gave the value of folding endurance. (Krishnaih Y.S.et al 2004)

2.5.5. Percentage moisture content

The prepared transdermal films were individually weighed and stored in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and the percentage moisture content was determined from the following formula.

$$\% \text{ Moisture content } = \frac{\text{Final weight X 100}}{\text{Final weight}}$$

2.5.6. Percentage moisture uptake

The films were weighed accurately and placed in the desiccators at room temperature for 24 hrs and then exposed to 84% RH using a saturated solution of potassium chloride. The films were weighed repeatedly until they showed a constant weight.

$$\% \text{ Moisture uptake } = \frac{\text{inal weight – Initial weight X 100}}{\text{Initial weight}}$$

2.5.7. Drug Content

The drug content in the formulation was assessed by blending the formulation with methanol, subjecting it to sonication for 10 minutes to achieve a clear solution, and subsequently filtering it. The resulting filtrate was then analyzed for drug content using a UV spectrophotometer at the wavelength maximum (λ max) of 284 nm.The average reading of three patches has been took as the content of drug in one patch. (Rhaghuram et al., 2003).

2.5.8. In- vitro drug release study

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ± 0.5 ^{0}C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer. The experiment is to be performed in triplicate and the mean value can be calculated (Singh et al., 1993).

3. Results and discussion

The present aim of this work is to formulate and evaluate transdermal patch of carbamazepine with using Hydroxy propyl methyl cellulose E15, Eudragit RL100, Ethyl Cellulose as a Polymers. The prepared formulations were evaluated for their Physical appearance, Uniformity of weight, Thickness, Folding endurance, Percentage moisture content, Percentage moisture uptake, Drug content and In vitro drug release study by using standard procedure. All studies were carried out in triplicate and average values were reported.

3.1. Preformulation Parameters

Table2 Analytical report for Carbamazepine

S.No	Test	Results
1	Appearance	White Colour
2	Odour	Odourless
3	Nature	Crystalline Powder
4	Solubility	Practical insoluble in water; soluble in alcohol, acetone and propylene glycol
5	Melting Point	189 ^{0}C

3.2. Drug - Excipient Compatability Tests

The compatibility studies were done in order to check any kind of interaction of carbamazepine , polymers and other excipients used in the formulation of patch.

FT-IR spectra of carbamazepine showed the following major peaks at 1682 cm^{-1} indicating -C-O stretching, a peak at 1321 cm^{-1} representing C-N stretching of tertiary amine and a peak at 3476 cm^{-1} representing –OH stretching. The formulations clearly showed the retention of these characteristic peaks of carbamazepine thus the results proved the absence of any interaction between the selected drug i.e., carbamazepine, polymers as well as other Excipients.

Table 3 FTIR Report for Carbamazepine

Wave Number(cm^{-1})	Functional Group
2960-2850	C-H Streching (alkane)
1700-1725	C-O Streching (acid)
1200-1500	C=N stretching (alcohol)
3300-2600	NH stretching

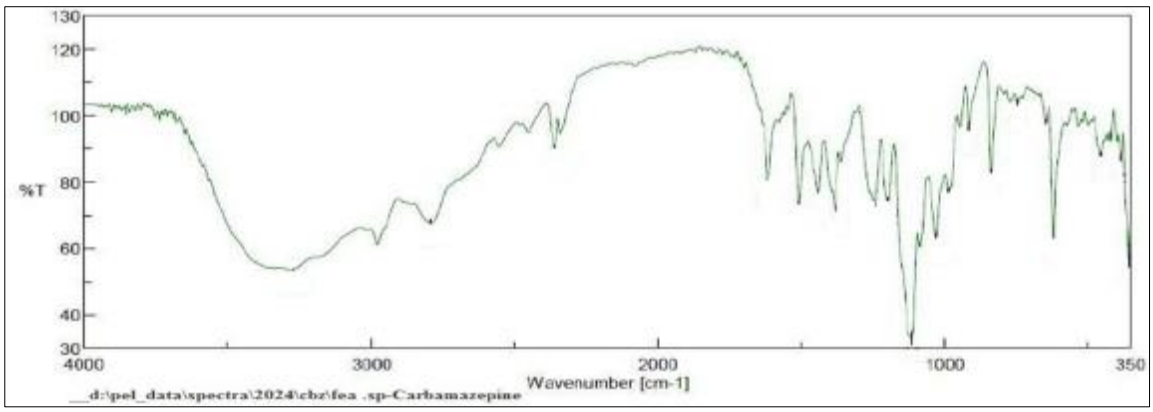

Figure 2 FT-IR spectra for Carbamazepine

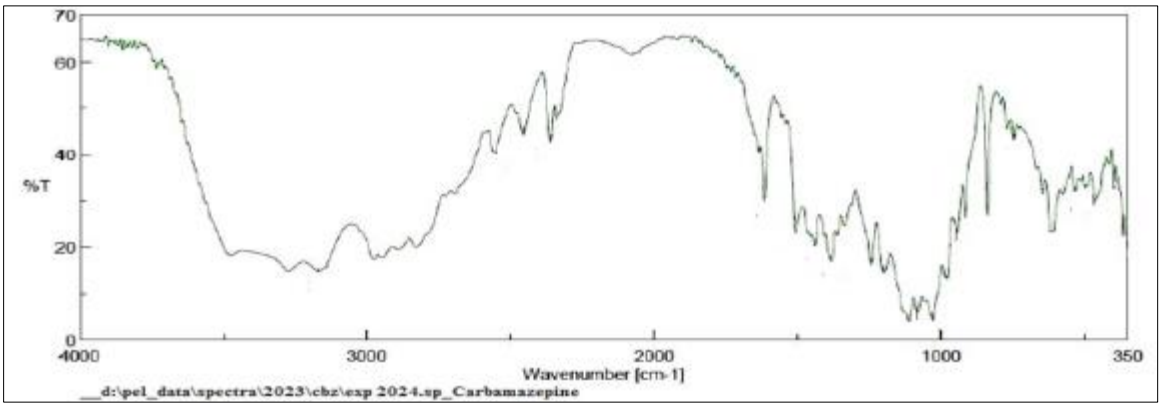

Figure 3 FT-IR spectra for Carbamazepine + Entire all polymers

3.3. Standard curve of Carbamazepine

In this study at 284 nm in pH phosphate buffer had good reproducibility in the concentration between 10 – 50 µg/ml. Correlation (R^2 = 0.998) between concentration and absorbance was found to be closer to 1 indicating that the method obeyed Beer - Lambert's law. After that, all concentrations were measured using a UV spectrophotometer with a maximum wavelength of 284nm.

Table 4 Standard calibration curve of Carbamazepine

Concentration (µg/ml)	Absorbance at 284 nm (in PBS, pH 7.4)
10	0.211
20	0.431
30	0.641
40	0.823
50	1.079

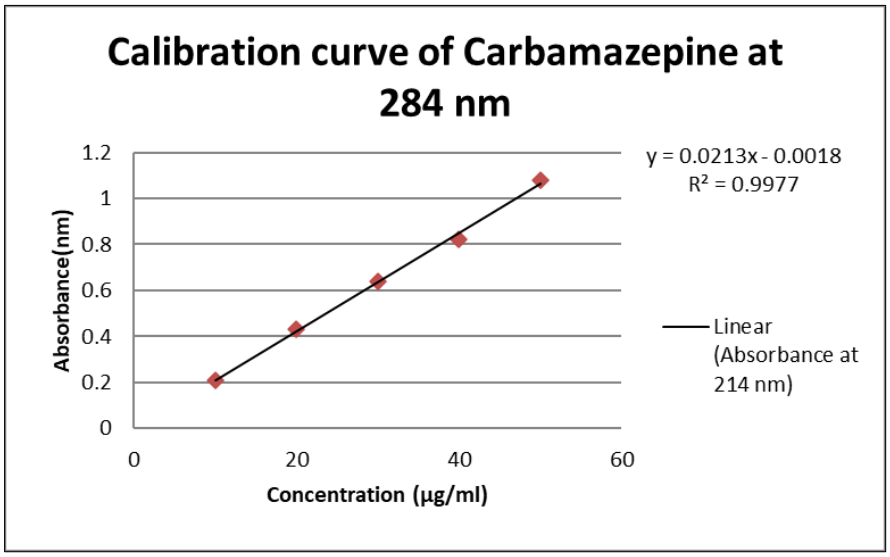

Figure 4 Calibration curve of Carbamazepine at 284 nm

Table 5 Physico Chemical Properties of Transdermal Patch of Carbamazepine

Formulations	Appearance	Weight Variation (mg)	Thickness (µm)	Folding Endurance	MoistureContent (%)	Moisture Uptake (%)	Drug Content (%)
F1	Smooth, Flexible	0.532 ± 0.0138	0.48 ± 0.031	82±0.011	1.3±1.3	5.1±2.9	89.7±0.77
F2	Smooth, Flexible	0.548 ± 0.0114	0.51 ± 0.022	89±0.021	1.9±0.8	5.6±3.16	91.8±0.85
F3	Smooth, Flexible	0.567 ± 0.0129	0.54 ± 0.042	97±0.016	2.1±1.6	7.4±1.12	94.2±0.54
F4	Smooth, Flexible	0.545 ± 0.0131	0.49 ± 0.034	85±0.013	1.4±0.5	5.3±2.1	90.1±0.17
F5	Smooth, Flexible	0.538 ± 0.0114	0.52 ± 0.053	88±0.021	1.8±1.2	5.9±2.66	92.9±0.32
F6	Smooth, Flexible	0.527 ± 0.0129	0.55 ± 0.012	99±0.036	2.5±1.8	7.6±2.21	96.2±0.67
F7	Smooth, Flexible	0.515 ± 0.0131	0.47 ± 0.019	81±0.041	1.1±1.3	5.1±1.3	88.1±0.72
F8	Smooth, Flexible	0.597 ± 0.0129	0.49 ± 0.032	87±0.061	1.7±0.6	5.7±3.12	92.2±0.62
F9	Smooth, Flexible	0.565 ± 0.0131	0.51 ± 0.046	93±0.043	1.9±1.9	7.1±1.91	93.1±0.17

Reported as mean ± S.D. (n=3)

Table 6 *In-Vitro* Drug Release Studies of Transdermal Patch of Carbamazepine

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
30 min	3.81	4.58	5.52	4.31	5.38	5.95	3.98	4.85	5.25
1 hr	13.25	15.96	18.47	12.02	14.23	17.47	16.25	17.09	19.96
2 hr	16.17	17.32	21.43	19.66	22.01	23.48	19.17	18.96	20.32
3 hr	18.17	19.32	24.48	22.61	27.16	29.48	20.17	21.66	24.32
4 hr	25.34	27.21	33.95	29.47	32.26	34.15	23.84	27.21	29.21
5 hr	32.47	34.25	41.86	36.41	39..61	41.86	33.47	37.31	39.25
6 hr	37.19	42.85	51.89	43.34	46.81	49.19	35.49	46.92	48.35
7 hr	41.72	48.24	58.14	49.78	52.41	56.14	40.27	49.62	52.24
8 hr	47.21	53.14	67.36	55.91	57.12	66.36	45.21	57.19	59.21
9 hr	50.21	55.42	69.61	59.61	59.81	69.92	54.21	62.89	65.34
10 hr	59.16	69.24	79.14	69.46	73.64	79.84	57.36	69.82	70.64
12 hr	74.91	78.95	85.75	77.61	86.83	93.95	72.41	77.93	83.52

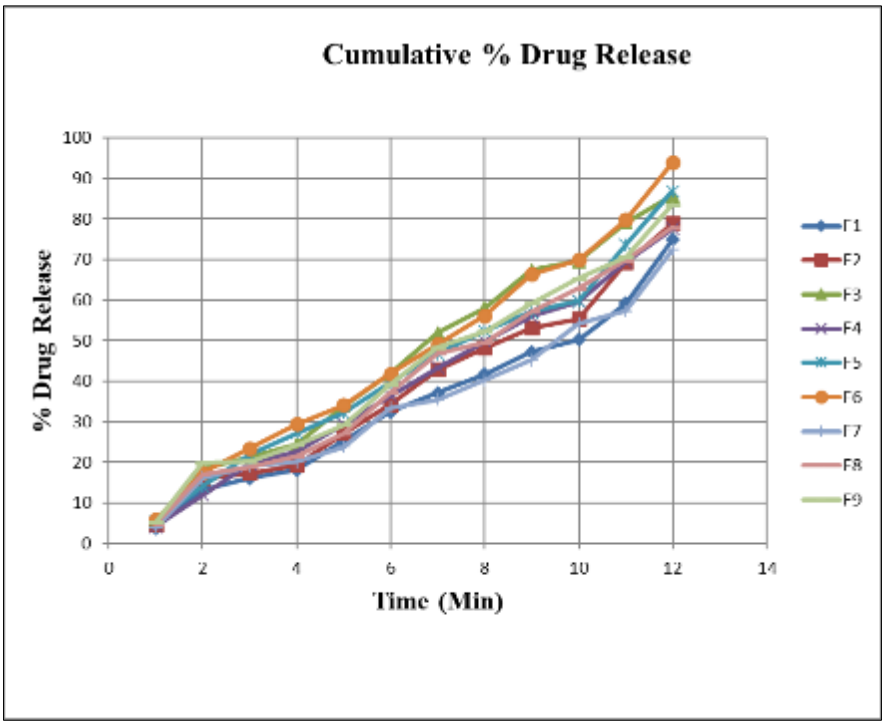

Figure 5 *In vitro* release profile of Transdermal Patch of Carbamazepine (F1- F9)

4. Conclusion

- Carbamazepine is an Antiepileptic and Anticonvulsants used to treatment of Epilepsy. It can be concluded from the present investigation that proper selection of polymers and drug is a prerequisite for designing and developing a Transdermal patch.
- In the present study, an attempt was made to formulate a transdermal matrix type patch of carbamazepine for efficient delivery of drug across the skin. To avoid first pass metabolism, gastro irritability and with better patient compliance. Various Nine formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were developed by using suitable polymer such as HPMC E15, Eudragit RL 100 and Ethylcellulose.
- The formulations were subjected for various physiochemical and characteristic test and *in-vitro* drug release test and the results were all under acceptable range.
- The FT-IR studies revealed that there was no chemical interaction of pure drug (Carbamazepine) with the polymers and excipients i.e. HPMC E15, Eudragit RL 100 and Ethylcellulose were found to be compatible with drug and excipients.
- All the Developed formulations were evaluated for various physiochemical parameters like Physical appearance, Uniformity of weight, Thickness, Folding endurance, Percentage moisture content, Percentage moisture uptake, Drug content and In vitro drug release studies...
- However, from the above results all the drug-loaded transdermal patches were found to be quite uniform in thickness, weight variation, Folding endurance, Percentage moisture content, Percentage moisture uptake, Drug content.
- Among the above all formulation F6 was chosen as a best Formulation, because this optimised formulation showed satisfactory drug content, physical characteristic for its thickness, weight uniformity, percentage moisture content, percentage moisture uptake, and maximum % of drug release i.e., 93.95 % in 12 hours.
- Hence formulation F6 showed best results because all the parameter showed satisfactory results it is considered as optimized formulation.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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