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RESEARCH ARTICLE

Formulation Development and *In-vitro* Characterization of Scopolamine Transdermal Patches

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ABSTRACT

In present study transdermal drug delivery of Scopolamine was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Matrix type of transdermal patches was developed by using polymers Eudragit polymers Transdermal patches were prepared by employing solvent casting method. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F9, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be within the pharmacopeial limits, in-vitro drug release studies by using dialysis membrane. Among all the 12 formulations F9 formulation which contains Eudragit S-100 and Eudragit L-100 200mg each had shown 99.6% cumulative drug release within 8 hours.

Keywords: Scopolamine, Transdermal patches, Eudragit S-100, Eudragit L-100

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CONTENTS

1. Introduction

Controlled drug delivery: Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release. The term controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other[1].the difference between sustained release and controlled release is shown by fig.1.

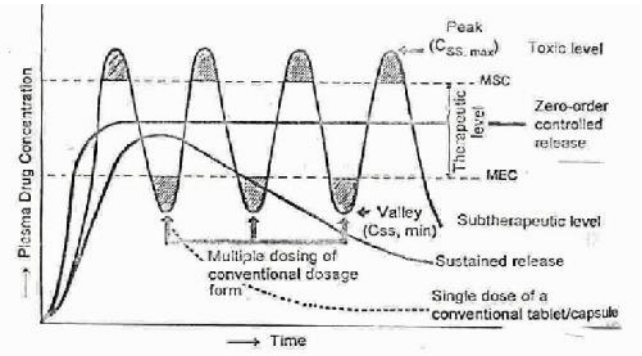


Figure 1: Comparative graphs of conventional, sustained & controlled release delivery systems.

Transdermal drug delivery: an Introduction

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation. Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Definition:

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

Skin pathways for transdermal drug delivery systems

When drugs are applied on the skin surface, penetration into and through the skin can occur via various routes. Drugs penetrate either via the stratum corneum (transepidermal) or via the appendages (transappendageal) (Figure 3 and 4). During penetration through the stratum corneum, two possible routes can be distinguished[11]. Penetration alternating through the corneocytes and the lipid lamellae (transcellular route). Penetration along the tortuous pathway along the lipid lamellae (intercellular route).

Steps Involved in Drug Transport from TDDS through the Skin: The various steps involved in transport of drug from patch to systemic circulation are as follows:

Diffusion of drug from drug reservoir to the rate controlling membrane. Diffusion of drug from rate limiting membrane to stratum corneum. Sorption by stratum corneum and penetration through viable epidermis: The structure of stratum corneum is often compared with a brick wall, with the corneocytes as the bricks surrounded by the mortar of the intercellular lipid lamellae. Uptake of drug by capillary network in the dermal papillary layer. Effect on target organ.

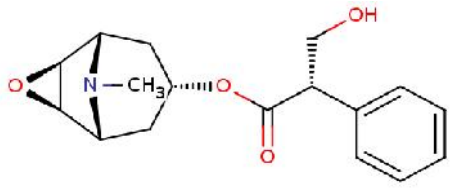
Basic components of transdermal drug delivery systems

The components of transdermal devices include:

a) Polymer matrix or matrices
b) The drug
c) Permeation enhancers
d) Other exciepients

Drug Profile

Drug:*Scopalamine*
Solubility:Sparingly soluble in water and methanol
Physicalstate:solid
Meltingpoint: 59 °C
Structure:



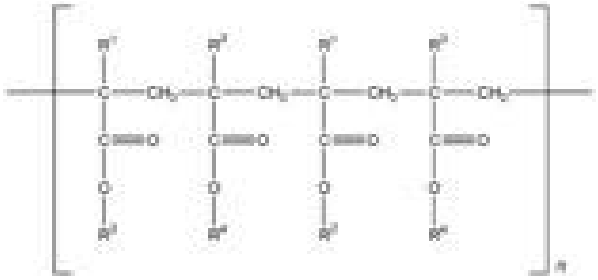
Molecular formula:$C_{17}H_{21}NO_4$
Molecular weight: Average:303.3529
Category: Muscarinic Antagonists, Adjuvants, Antispasmodics

Excipients Profile:

Eudragilt-L100

Synonyms: Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates.

Chemical name: Poly (butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate).
Empirical formula: $C_5\ H_8\ O_2$
Molecular weight: ≥100 000
Structural formula:



Functional category: Film former; tablet binder; tablet diluent.

Propylene Glycol

Nonproprietary Names: Propylene glycol
Synonym: 1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol.
Chemical Name: 1,2-Propanediol [57-55-6] (−)-1,2-Propanediol
Empirical Formula: $C_3H_8O_2$

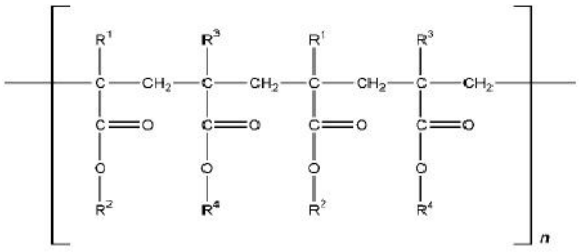
Molecular Weight: 76.09

Functional Category: Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible co-solvent.

Eudragit S 100

IUPAC name: Poly (methacylic acid-co-methyl methacrylate) 1:2

Structure:



For Eudragit S: R_1, $R_3 = CH_3$ $R_2 = HR_4 = CH_3$

Chemical name: Poly (methacrylic acid, methyl methacrylate) 1:2

Types: Eudragit S 12.5, Eudragit S 12.5 P

Description: Fine white powder or creamy-white granules

2. Materials and Methods

Table 1: List of Materials

S.No	Material Name
01	Eudragit-L100(mg)
02	Eudragit-S100(mg)
03	Dimethyl formamide (ml)
04	Ethanol(ml)
05	Propylene glycol(Drops)
06	PEG 400(Drops)

Table 2: List of Equipment's

S.No.	Instruments	Manufacturer
1.	Digital weighing balance	Wensar
2.	Digital pH meter, cyber pH-14L	Lab India
3.	Franz diffusion cell	Borosil
4.	Glassware	Borosil, Mumbai, India.
5.	UV-Spectrophotometer	Lab India

I. Preformulation study:

Preformulation studies were primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

Selection of drug and other ingredients:

Scopolamine was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Transdermal drug delivery system. Eudragit-L100, Eudragit S-100 were selected as matrix forming polymers. Propylene glycol and PEG 400 were selected as permeation enhancer and plasticizer.

Preparation of Phosphate Buffer pH 7.4:

Accurately measured 250 ml of 0.2 M potassium dihydrogen phosphate in a 1000 ml of volumetric flask and added 195.5 ml of 0.2 M sodium hydroxide and then water was added to make up the volume and adjusted pH 7.4 by using 0.2 M potassium dihydrogen phosphate/sodium hydroxide.

Construction of standard graph of Scopolamine:

Standard graph of Scopolaminewas plotted in PBS pH 7.4. Scopolaminewas estimated spectrophotometrically at λ_{max} of 270 nm.

Preparation of standard solution: Stock solution-I was prepared by dissolving Scopolamine100 mg in 100 ml of buffer, so as to get a solution of 1 mg/ml concentration. Then stock solution - II was prepared by taking 10 ml from the previous stock solution i.e. stock solution - I and dissolved in 100 ml of buffer, so as to get a solution of 100 µg/ml concentration. Accurately measured aliquot portions of standard drug solution, from stock solution -II were taken, like 0.8 ml, 1ml, 1.2ml, 1.4 ml and 1.6 ml were transferred in to 10 ml volumetric flasks and were diluted up to the mark with buffer pH 7.4. Absorbance of each solution was measured at λ_{max} of 270 nm against buffer pH 7.4 as the blank, by using UV-spectrophotometer. A graph was plotted by taking concentration of drug vs absorbance was plotted.

II. Formulation:

Development of Transdermal patches:

Transdermal drug delivery patches were prepared by solvent casting method.

Solvent casting method:

Transdermal patches were prepared according to the formula shown in Table 08. Eudragit L100, Eudragit S100 were weighed in requisite ratios and they were then dissolved in dimethyl formamide and ethanol as solvent using magnetic stirrer. Scopolamine (100mg) with a magnetic stirrer. Propylene glycol and PEG 400 was added to the above dispersion under continuous stirring. The uniform dispersion was poured in the petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches. After 24h, the dried films were taken out and stored in desiccator.

III. A) Evaluation of Transdermal patch by physical methods:

- Moisture content
- Physical appearance
- Thickness
- Weight variation
- Flatness
- Folding endurance
- Moisture uptake
- Drug content determination

B) Evaluation of Trandermal patch by permeation studies:

- Diffusion cell
- In vitro permeation studies using dialysis membrane
- Kinetic modeling of drug release
  1. **Zero order release model**
  2. **First order release model**
  3. **Higuchi's Release Model**
  4. **Korsmeyer-peppas release model**

Drug excipients interaction studies - FT-IR spectrum interpretation

3. Results and Discussion

Evaluation of Scopolamine Transdermal patches:

Physical appearance:

All the Transdermal patches were visually inspected for color, clarity, flexibility.

Flatness:

All the Transdermal patches were found to be flat without any foam. The prepared Scopolamine Transdermal patches were evaluated for their physical parameters such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and all the results were found to be were found to be within the pharmacoepial limits.

Table 3: Standard graph of Scopolamine

Concentration (µg/ml)	Absorbance
0	0
2	0.295
4	0.203
6	0.301
8	0.417
10	0.528
12	0.653
14	0.771
16	0.881

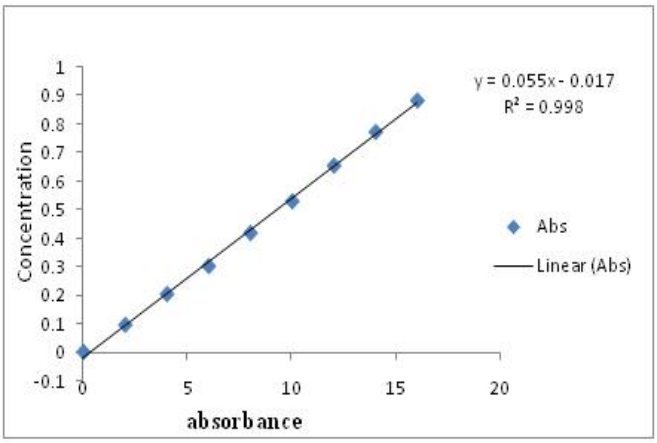


Figure 1: Standard curve of Scopolamine

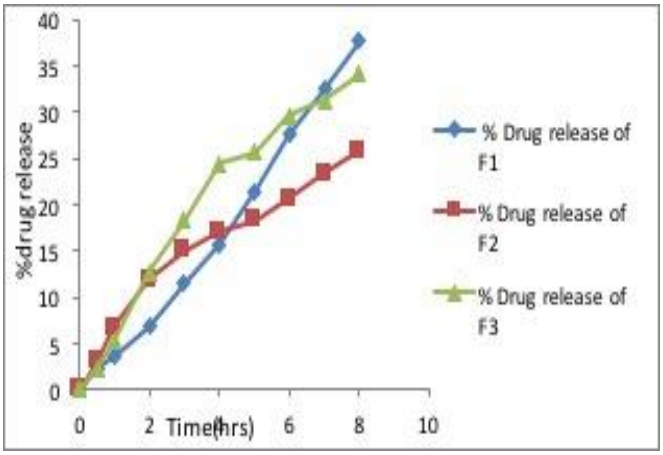


Figure 2: % drug release of F1, F2, F3

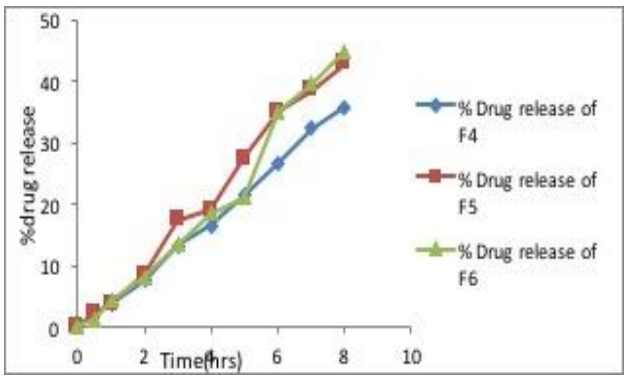


Figure 2: % drug release of F4, F5, F6

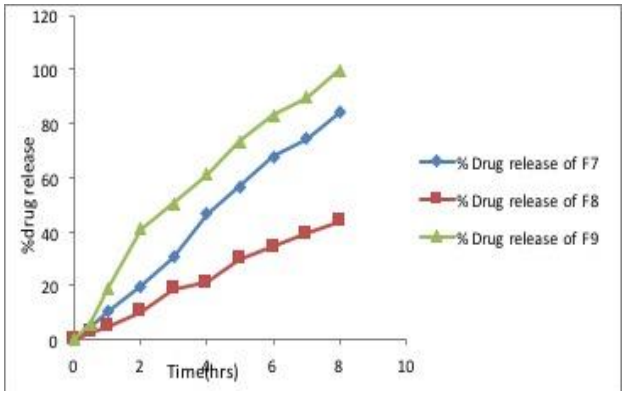


Figure 3: % drug release of F7, F8, F9

The prepared Scopolamine Transdermal patches were evaluated for In-vitro permeation studies using dialysis membrane, among all the 9 formulations F9 formulation was shown 99.6% cumulative drug release within 8 hours.

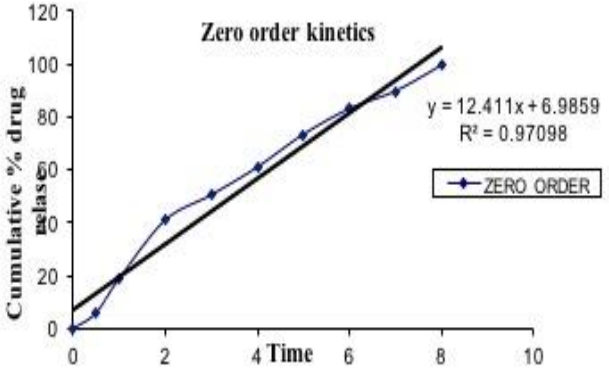


Figure 4: Zero order kinetics

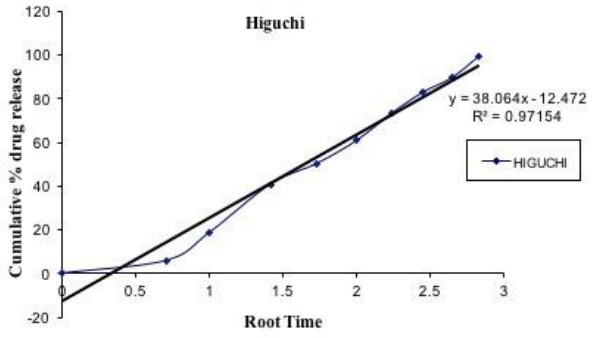


Figure 5: Higuchi plot

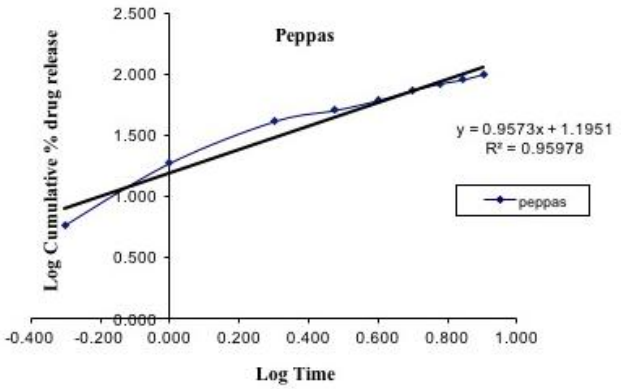


Figure 6: Peppas plot

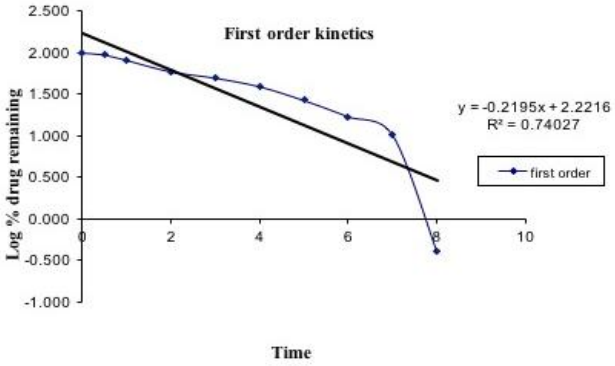


Figure 7: First order kinetics

The kinetics of In-vitro permeation studies using dialysis membrane for F12 formulation was plotted and the F12 formulation followed the Higuchi mechanism of drug release.

Drug excipients interaction studies:

FT-IR spectrum interpretation: IR spectral analysis was carried out using FT-IR by the KBr disc method and the results showed that there are no interactions between drug and excipients. The results were attached in the Annexure.

4. Conclusion

In present study transdermal drug delivery of Scopolamine was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Matrix type of transdermal patches was developed by using polymers Eudragit polymers Transdermal patches were prepared by employing solvent casting method. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F9, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be within the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 12 formulations F9 formulation which contains Eudragit S-100 and Eudragit L-100 200mg had shown 99.6% cumulative drug release within 8 hours.

Table 4: Formulations of Scopolamine Transdermal Patch

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug(mg)	100	100	100	100	100	100	100	100	100
2	Eudragit-L100(mg)	100	200	300	400					200
3	Eudragit-S100(mg)					100	200	300	400	200
4	Dimethyl formamide (ml)	15	15	15	15	15	15	15	15	15
5	Ethanol(ml)	10	10	10	10	10	10	10	10	10
6	Propylene glycol(Drops)	5	5	5	5	5	5	5	5	5
7	PEG 400(Drops)	20	20	20	20	20	20	20	20	20

Table 5: Evaluation of Scopolamine Transdermal patch by physical methods

Cumulative (%) release Q	Time (T)	Root (T)	Log (%) release	Log (T)	Log (%) remain	Releaserate (cumulative % release/t)	1/cum% release	Peppaslog Q/100	% drug remain	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
5.86	0.5	0.707	0.768	-0.301	1.974	11.720	0.1706	-1.232	94.14	4.642	4.549	0.092
18.7	1	1.000	1.272	0.000	1.910	18.700	0.0535	-0.728	81.3	4.642	4.332	0.310
40.9	2	1.414	1.612	0.301	1.772	20.450	0.0244	-0.388	59.2	4.642	3.895	0.746
50.5	3	1.732	1.703	0.477	1.695	16.833	0.0198	-0.297	49.5	4.642	3.672	0.970
61.0	4	2.000	1.785	0.602	1.591	15.250	0.0164	-0.215	39	4.642	3.391	1.250
73.4	5	2.236	1.866	0.699	1.425	14.680	0.0136	-0.134	26.6	4.642	2.985	1.656
83.1	6	2.449	1.920	0.778	1.228	13.850	0.0120	-0.080	16.9	4.462	2.566	2.075
89.8	7	2.646	1.953	0.845	1.009	12.829	0.0111	-0.047	10.2	4.642	2.169	2.473
99.6	8	2.828	1.998	0.903	-0.398	12.450	0.0100	-0.002	0.4	4.642	0.737	3.905

Table 6: Evaluation of Scopolamine Transdermal patch by In-vitro permeation studies using dialysis membrane

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
F1	590.2	0.569	20	65	7.98	3.77
F2	598.3	0.520	25	65	25.05	9.2
F3	599.5	0.570	27	57.5	13.09	5.16
F4	598.3	0.596	24	60	15.63	5.66
F5	599.6	0.560	30	67.5	11.73	4.87
F6	593.1	0.517	32	92.5	19.65	12.67
F7	589.5	0.578	40	99.7	9.42	3.43
F8	591.1	0.537	37	85	10.87	4.72
F9	600	0.503	44	100	6.44	3.62

Figure 8: FTIR of pure drug

Figure 9: FTIR of optimised formulation

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