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FORMULATION AND EVALUATION OF CARVEDILOL BY TRANSDERMAL PATCHES DRUG DELIVERY SYSTEM

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ABSTRACT

The formulation and evaluation of Carvedilol transdermal patches as a drug delivery system were carried out to enhance its bioavailability, overcoming the limitations of oral administration. Transdermal Drug Delivery Systems (TDDS) are effective in ensuring continuous and controlled drug release, offering advantages like bypassing the first-pass metabolism, improving patient compliance, and maintaining stable blood concentrations. Carvedilol, a non-selective beta-blocker, was formulated into patches using a combination of HPMC K4M and Eudragit RL100 polymers by the solvent evaporation method. The prepared patches were evaluated for various physicochemical properties such as weight variation, thickness, tensile strength, moisture content, and adhesion tests. Scanning Electron Microscopy (SEM) was utilized to examine the surface morphology of the patches, both before and after the penetration study. The results indicated that the patches exhibited desirable characteristics for transdermal drug delivery, suggesting potential benefits for improving bioavailability and therapeutic efficacy of Carvedilol. Further in vivo studies are necessary to validate the findings and optimize the formulation.

KEYWORDS: Carvedilol, Transdermal Patches, Solvent Evaporation, Adhesive Properties.

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) refer to formulations created to administer an appropriate medicinal dosage through a patient's skin, ensuring the delivery of a therapeutic

dose of the drug into the body. In order to achieve systemic effects by transmitting therapeutic substances through human skin, it is essential to consider the skin's biophysical, morphological, and physicochemical properties comprehensively. Transdermal drug delivery presents notable advantages compared to injectables and oral routes, as it improves patient compliance and circumvents the first-pass metabolism.

It ensures a controlled and consistent drug administration, particularly beneficial for drugs with short biological half-lives, preventing abrupt entry into the systemic circulation that often leads to adverse effects. As a result, various innovative drug delivery systems, such as transdermal drug delivery systems, transmucosal delivery systems, and controlled release systems, have been developed. The benefits of transdermal drug delivery include improved therapeutic efficiency, reduced hepatic first-pass metabolism, and the maintenance of a stable drug concentration in the bloodstream. The first transdermal system was FDA-approved in 1979 for preventing nausea and vomiting. Confirmation of percutaneous drug absorption can be established through measurable blood levels, detecting excretion of the drug and its metabolites in urine, and observing the patient's clinical response to the administered drug therapy.

A transdermal patch is a specialized medicated patch designed to release drugs into the bloodstream at a controlled rate through the layers of the skin. These patches offer a highly convenient method of drug administration, as they are painless and can provide continuous treatment for several days. Additionally, they can be easily discontinued at any time. Transdermal patches come in various sizes and can contain multiple active ingredients. When applied to the skin, these patches use diffusion processes to deliver these active ingredients directly into the systemic circulation. Some patches may contain high doses of the active constituent, which remains on the skin for an extended period. Nitroglycerin was the first transdermal patch developed in 1985, marking a significant milestone in this drug delivery method. Gale and Berggren developed patches that incorporate a rate-controlling ethylene vinyl acetate membrane. Various drugs are formulated as transdermal patches, such as nicotine, estradiol, fentanyl, clonidine, scopolamine (hyoscine), and estradiol with norethisterone acetate. The specific site of patch application depends on the type of drug therapy. For instance, estradiol patches are typically placed around the buttocks or abdomen, while nitroglycerin patches can be applied around the chest area. The duration of drug release

varies, ranging from as short as 9 hours to as long as 9 days, depending on the intended usage.

Fig.1: Transdermal Patch

1.1 Advantages of TDDS

- To prevent first-pass metabolism, transdermal delivery ensures a sustained and continuous permeation of a substance over an extended period.
- Increase Patient compliance.
- It does not interfere the liquid of the stomach and intestines.
- Sustains stable and constant blood levels, providing control over an extended period.
- Reduced plasma concentration levels of drugs.

1.2 Disadvantages of TDDS:

- High drug levels in Blood/ plasma could not be achieved.
- Large molecular size of drugs cannot be formulated.
- Possibility of inflammation on the site of application.
- Not comfortable to wear.
- May not be economical.

1.3 Skin Structure

Indeed, the skin is the body's largest organ, acting as a crucial protective barrier safeguarding the body from a range of external factors and potential threats. Its large surface area, approximately 1.7 square meters in an average person, allows it to effectively shield the body

from microorganisms, ultraviolet (UV) radiation, chemicals, allergens, and water loss. This protective function is vital for maintaining overall health and well-being. Additionally, the skin also plays a role in regulating body temperature, sensation, and the synthesis of vitamin D through exposure to sunlight. Taking care of the skin is essential to support its functions and maintain good health. The skin is commonly categorized into three primary layers: The outermost layer, known as the epidermis; (b) The middle layer, referred to as the dermis; and (c) The innermost layer, called the hypodermis.

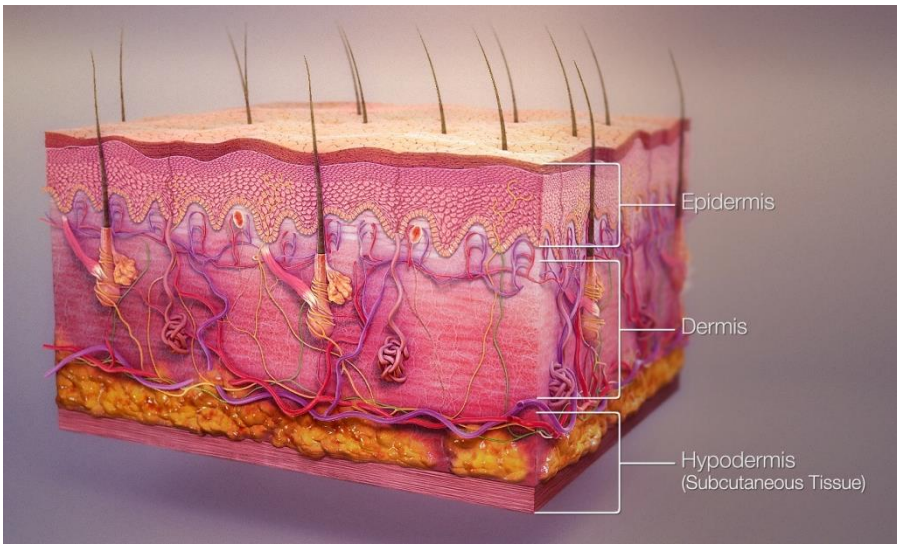


Fig. 2: Human Skin.

2. DRUG PROFILE

CARVEDILOL

Table 1: Drug Profile.

IUPAC Name	1-(9H-carbazole-4yloxy)-3-{[2-(2-methoxy phenoxy)ethyl]amino}propan-2-ol
Chemical Formula	C24H26N2O4
Water Solubility	Practically insoluble (0.583 mg/L)
Molecular Weight	406.4742
Melting Point	114.5°C
Bioavailability	25-35%
Protein Binding	98%
Metabolism	Liver (CYP2D6, CYP2C9)
Biological Half Life	7-10 hours
Clearance	500-700 ml/min
Excretion	Urine (16%), feces (60%)

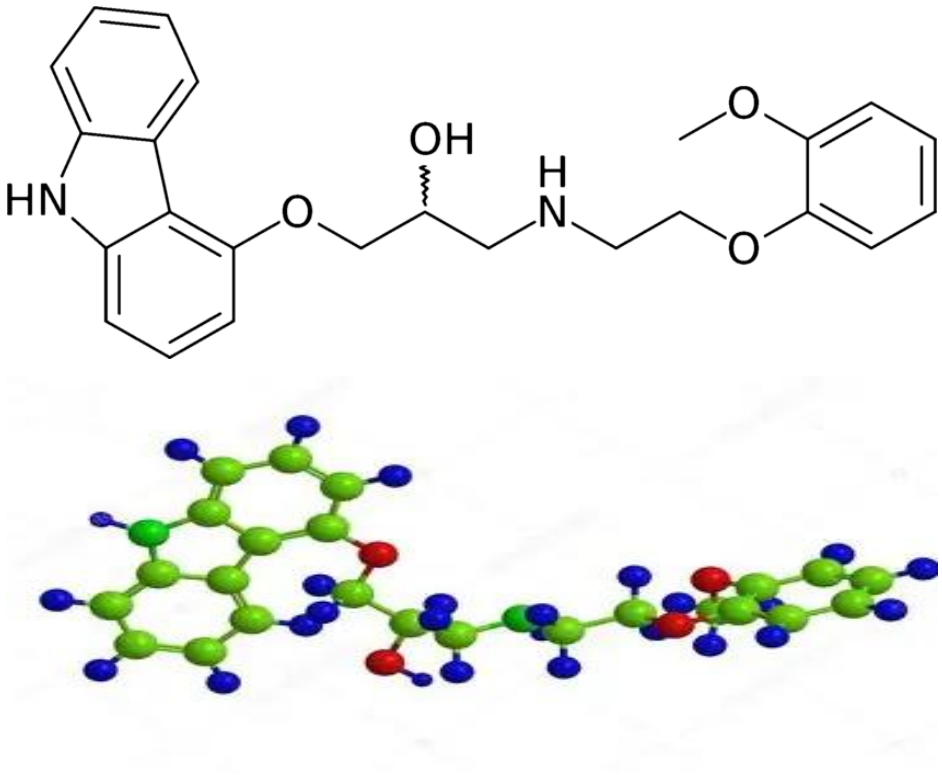


Fig. 3: Structure Of Carvedilol.

3. MATERIALS AND EQUIPMENTS:

3.1 Identification & Selection Of Excipients:

HPMC K4 M solution acts to swell and absorb water, thereby expanding the thickness of the tear- film It is a semi synthetic, inert, viscoelastic polymer, exhibits a thermal gelatin property, non-flowable, semi flexible mass used as excipient incontrolled oral medicaments and a varietyof ophthalmic products. It has wide used in pharmaceutical, food, cosmetics, and eye drops. The HPMC K4M film has an ability of ductility, toughness and elasticityin the physiochemical property. Thusit provides excepted controlled release of the drug offering increased permeability properties. EUDRAGIT RL 100 is a co-polymer of ethyl acrylate, methyl methacrylateand a low content of methacrylic acid ester with quaternary ammonium group The ammonium groups are present as salts and make the polymers permeable. It is used in varieties of targeted drug release,time controlledrelease, pH independent release studies and it forms easy and suitable for matrix structures and hence selected in transdermal drug delivery system.

3.2 Preparation Of Carvedilol Transdermal Patches Using Solvent Evaporation Method

Transdermal patches of Carvedilol were prepared by solvent evaporation technique for the formulations. Solution of HPMC K4M and Eudragit RL100 were prepared separately in

dichloromethane methanol (1:1) mixture. The two polymeric solutions were mixed to which weighed amount of carvedilol was added slowly to the mixture. A drop of glycerin(0.25ml) and permeation enhancer (oleic acid/DMSO/DMF) were added and mixed. The drug polymer solution was casted in aluminum mould of cm^2, which is wrapped by aluminum foil. The mould was kept aside for drying at room temperature for 24 hours inverted funnel was placed over the mould to prevent the current of air. After drying, the patches were carefully peeled from the mould wrapped in aluminum foil, and preserved in desiccator for further studies.

Table 2: Preparation Of Transdermal Patches Of Carvedilol.

Formulation	T1	T2	T3	T4	T5	T6
Carvedilol (mg)	50	50	50	50	50	50
HPMCK4M(15CPS) (mg)	300	200	150	150	150	150
Eudragit RL 100(ml)	-	100	150	150	150	150
Glycerin (4 drops) (ml)	0.25	0.25	0.25	0.25	0.25	0.25
Dichloromethane: methanol	7	7	7	7	7	7
Oleic acid(ml)	-	-	-	0.25	-	-
DMSO (ml)	-	-	-	-	0.25	-
DMF(ml)	-	-	-	-	-	0.25

(-) = No ingredient

DMSO= Dimethyl Sulphoxide

HPMC= Hydroxypropyl methyl cellulose

DMF = Dimethyl formamide

3.3 Evaluation Of Carvedilol Transdermal Patches:

1. Physical appearance
2. Weight variation
3. Thickness of the patches
4. Tensile strength
5. Flatness
6. Percentage elongation break test
7. Folding endurance
8. Moisture content
9. Moisture uptake
10. Percent water vapor transmission rate (PWVTR)
11. Thumb tack test
12. Rolling ball tack test

13. Quick stick test

14. Probe tack test

15. SEM Analysis

4. RESULT AND DISCUSSION

4.1 Physical Appearance:

All the transdermal patches films are visually inspected for color, clarity, flexibility, and smoothness in appearance.

4.2 Weight Variation

Table 3: Weight Variation.

Formulation	Trail1	Trail 2	Trail 3	Mean ± S.D
T1	0.042	0.044	0.042	0.0462±0.016
T2	0.035	0.033	0.033	0.0336±0.0016
T3	0.033	0.030	0.031	0.0313±0.0015
T4	0.034	0.034	0.032	0.0333±0.0016
T5	0.035	0.032	0.034	0.0336±0.0015
T6	0.034	0.032	0.033	0.033±0.001

S. D = standard deviation of three determination.

4.3 Thickness

Table 4: Thickness.

Formulation	Trail 1 mm	Trail 2 mm	Trail 3 mm	Mean ± S. D
T1	0.22	0.2	0.21	0.21±0.001
T2	0.19	0.19	0.19	0.19±0.000
T3	0.17	0.18	0.17	0.1733±0.005
T4	0.18	0.18	0.18	0.18±0.000
T5	0.19	0.18	0.19	0.1866±0.005
T6	0.18	0.19	0.18	0.1833±0.005

4.4 Tensile Strength

Table: 5 Tensile Strength.

Formulation	Trail1	Trail 2	Trail 3	Tensile Strength (kg±S.D)
T1	2.842	2.831	2.850	2.841±0.009
T2	2.224	2.229	2.223	1.225±0.003
T3	1.692	1.699	1.702	1.697±0.005
T4	1.846	1.842	1.848	1.845±0.003
T5	1.823	1.827	1.821	1.823±0.003
T6	1.870	1.868	1.865	1.867±0.002

4.5 Flatness

Table 6: Flatness.

Formulation	PERCENTAGE OF FLATNESS			
	Trail 1	Trail 2	Trail 3	Mean ± S.D
T1	98.5	98.3	98.1	98.3±0.2
T2	97.4	97.1	97.2	97.23±0.153
T3	98	97.92	97.95	97.96±0.041
T4	98.1	98.5	97.9	98.17±0.305
T5	97.6	97.4	97.2	97.37±0.252
T6	98.4	98.2	98.5	98.37±0.153

4.6 Percentage Elongation Break Test

Table 7: Percentage Elongation Break Test.

Formulation Code	% ELONGATION BREAK TEST (mean ± S.D)
T1	35.8±0.012
T2	37.1±0.012
T3	41.2±0.015
T4	39.6±0.017
T5	40.1±0.013
T6	38.8±0.014

4.7 Folding Endurance

Table 8: Folding Endurance.

Formulation	Trail 1	Trial	Trial 3	Mean ± S.D
T1	150	165	158	157.66±7.505
T2	113	129	125	122.23±8.326
T3	82	76	88	82±6
T4	104	92	97	98±6.027
T5	75	76	67	72.66±4.932
T6	86	89	93	89.33±3.511

4.8 Percentage Moisture Loss:

Table 9: Percentage Moisture Loss.

Formulation	Trial 1	Trial 2	Trial 3	Mean ± S.D
T1	42.857	39.285	42.857	41.666±2.062
T2	11.111	11.111	14.814	12.345±2.137
T3	13.793	10.344	12.643	12.643±1.991
T4	9.677	6.451	9.6777	8.6016±1.862
T5	16.625	12.5	12.5	13.541±1.804
T6	18.75	12.5	12.5	14.582±3.608

4.9 Percentage Moisture Absorption

Table 10: Percentage Moisture Absorption.

Formulation	Trial 1%	Trial 2%	Trial 3%	Mean ± S.D %
T1	6.976	6.976	9.302	7.751±1.324
T2	2.587	8.571	8.571	6.666±3.298
T3	8.823	6.882	8.823	7.482±1.697
T4	12.121	16.151	9.09	12.12±3.03
T5	9.09	9.09	9.09	9.0. ±0.00
T6	9.375	12.5	9.375	10.416±1.815

4.10 Water Vapor Transmission Rate (WVTR)

Table 11: Water Vapor Transmission Rate.

Formulation	Trial 1	Trial 2	Trial 3	Mean ± S.D
T1	0.066	0.663	0.0066	0.0065±0.0001
T2	0.0072	0.6083	0.0063	0.0072±0.001
T3	0.0063	0.0046	0.0072	0.006±0.001
T4	0.0063	0.0075	0.0075	0.0071±0.0006
T5	0.00057	0.0075	0.008	0.007±0.0012
T6	0.0049	0.0077	0.0083	0.0069±0.0018

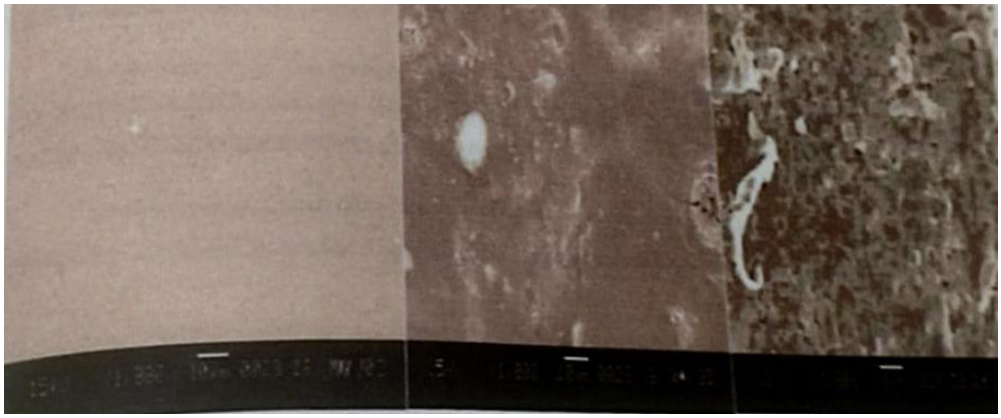
4.11 Evaluation Of Adhesive Layer

Table 12: Adhesive Layer.

Formulation	Thumb Tack Test	Rolling Ball Test (cm)	Peel Tack Test (sec)	Probe Stack Test (g)
T1	-	19.25±0.22	9.44±0.22	2.55±1.1
T2	+	12.66±0.66	11.88±0.55	1.88±0.12
T3	++	15.88±0.87	22.12±1.22	0.99±0.55
T4	+++	11.12±0.45	45.22±0.18	0.65±0.3
T5	++	17.88±0.42	38.22±0.12	0.88±0.24
T6	++	18.22±0.55	40.22±0.98	1.1±0.22

4.12 SEM Analysis

Fig. 4: SEM Analysis.



A B C

Scanning electron microscope (SEM) of blank & transdermal patches:

A: SEM of blank transdermal film (without drug)

B: SEM of carvedilol loaded transdermal film before carrying out the penetration study

C: SEM of carvedilol loaded transdermal film after carrying out the penetration studies.

5. CONCLUSION

Carvedilol transdermal delivery system as it complies withphysicochemical parameters suitable for skin penetration. From the above results, it is acknowledged that present work was an adequate preliminary study of improving bioavailability of carvedilol by transdermal patches using HPMC K4M- 15 and Eudragit RL 100. Further detailed investigation and elaborate in vivo and in vitro studiesneed to be carried out and need to be established to guarantee the efficiency and bioavailability of the formulation, Studies on improving bioavailability have to be carried out with different polymers. Various test such as drug uniformity, determination of surface PH folding endurance test, thickness of patches, weight of patches, moisture content, water absorption studies, tack properties, quick stick test, probe tack test, peel adhesive properties, tensile strength, shear strength properties, where carried to prove stability of the drug.

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