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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF CARVEDILOL

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ABSTRACT

Transdermal drug delivery system is being extensively investigated as a viable alternative to drug delivery with improved bioavailability. The aim of the present investigation is to develop membrane type Transdermal drug delivery patches of antihypertensive agent Carvedilol. Transdermal patches of Carvedilol were prepared by using polymers, like HPMC, Eudragit L100, and PVPK30. The patches were transparent, smooth and flexible. The results of weight variation, thickness, moisture content, moisture uptake, Folding Endurance, Tensile strength, drug content. It is evident that drug release is increased with the increase in concentration of HPMCK15M .

KEY WORDS: Carvedilol, Transdermal Patches, HPMCK15M, bioavailability.

1. INTRODUCTION

The decision to use transdermal drug delivery is based on the relative advantages and disadvantages for the patient. Advantages include the following: avoidance of the gastrointestinal (GI) tract irritation and hepatic first pass biotransformation and metabolism, control of absorption, availability of multiple skin sites to avoid local irritation and toxicity, and improve patient compliance. Carvedilol is the most widely prescribed drug in the long term treatment of hypertension, following oral administration, Carvedilol is rapidly absorbed from GIT(80%)but the oral bioavailability remains low (23%to35%) because of significance first pass metabolism by cytochrome $p_{450.}$ Carvedilol also has a short plasma half-life of 6hrs; long term therapy of hypertension by oral administration may result in poor patient compliance because of low bioavailability and short plasma life, leading to increased frequency of administration. Therefore an alternative route is needed for administration. The transdermal route is an alternative for administration of such drugs; this route offers many advantages over oral dosage forms, such as improving patient compliance in long term therapy, by passing first pass metabolism and sustaining drug delivery. Carvedilol has a short half-life of about 6hrs and requires frequent dosing in order to maintain the optimal therapeutic concentration and absolute bioavailability of Carvedilol is about 25% low oral bioavailability provide a rationale for developing a transdermal delivery system of Carvedilol**.**

2. MATERIALS AND METHODS

Carvedilol procured from Zydus Cadila,Ahmedabad, HPMCK4M, HPMCK15M, EudragitL100, PVPK-30 gift sample from Microadvanceresearch Centre,Bangalore, Glycerin, DMSO, Tween80 purchased from Finarchemicals Limited,Ahmedabad, Methanol purchased from Jiangsu Huaxi Internationaltrade Co Limited,China.

Fabrication of Cavedilol Patches: The membrane type transdermal patches containing Carvedilol prepared using HPMC alone and by using different ratios of HPMC and PVPK30, combination of HPMCK4M &eudragitlL100.the polymers were dissolved in suitable solvent in required amount mixed well by using magnetic stirrer. Carvedilol was added slowly to the polymer solution and mixed thoroughly to obtain uniform solution. Glycerin is used as plasticizer and DMSO and TWEEN80 were used as penetration enhancer. The polymeric solution was poured into petriplate placed in a level, hard rigid surface. Solvent evaporation was controlled by covering with placement of funnel in its inverted position. After 24hrs the films were removed and kept in desiccators. Then the films were cut in a circular disk with $2cm^2$ diameters. These films were wrapped in aluminium foil packed in self sealing cover and kept in desiccators. The composition of various formulations was given in the following table.

Physicochemical evaluation:

Thickness: The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight: 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.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole

solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Table.1.Formulation of Carvedilol patches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F10
Cavedilol	13	13	13	13	13	13	13	13	13
HPMCK 15M	300	350	400	450	500	450	400	300	-
PVPK 30	---	---	---	---	---	50	100	200	--
HPMC K4M	---	---	---	--	--	--	--	---	210
EUDRAGIT L100	--	---	----	---	---	---	----	---	90
Glycerin	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.12
DMSO									0.6
TWEEN 80	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	---
DCM + Methanol	20	20	20	20	20	20	20	20	---
Acetone	----	----	-----	----	---	---	---	----	20

Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

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

$$\% \text{ Moisture uptake} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1}$$

Folding endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

RESULTS

Table.2.Pre-formulation Studies of Carvedilol

Parameter	Standard	Result
Color	White or all most white	white
Odour	Pungent	pungent
State	Crystalline	solid, powder form
Solubility	Soluble in methanol, methelene chloride, Freely soluble in DMSO Sparingly soluble in alcohol	soluble in methanol, DMSO, acetone Insoluble in water, gastric fluid Sparingly soluble in ethanol
Melting Point	115-117^{0}c	116^{0}c
Partition coefficient	Octanol/water 0.56	Octanol/water bwas0.58, Octanol/phosphate buffer PH7.4 phosphate buffer was 0.61

Table.3.Post formulation studies of Carvidolol TDDS

Formulation Code	Weight variation	Thickness	%moisture absorbed	%moisture Loss	Folding endurance	Drug content
F1	0.3506±0.005	0.086±0.005	1.6±0.2	1.4±0.2	10	98
F2	0.3653±0.003	0.146±0.011	1.7±0.15	1.46±0.2	12	96
F3	0.3743±0.0025	0.1732±0.005	1.3±0.05	1.56±0.11	10	88
F4	0.4556±0.034	0.1833±0.003	1.5±0.25	1.63±0.25	11	85
F5	0.5136±0.021	0.19±0.01	2.16±0.11	2.3±0.11	12	88
F6	0.360±0.055	0.12±0.01	2.23±0.15	1.43±0.15	10	101
F7	0.324±0.055	0.12±0.01	1.73±0.15	1.56±0.152	12	104
F8	0.238±0.01	0.06±0.03	1.6±0.1	1.36±0.05	13	106
F9	0.251±0.015	0.12±0.005	1.4±0.2	1.2±0.1	12	93
F10	0.2006±0.004	0.11±0.025	1.2±0.15	0.86±0.67	10	82

Table.4.Cumulative % Durg Release of Formulations F1 To F10

Time (Hours)	Cumulative % durg release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
1	1.73	1.8	1.87	2.7	2.8	4.3	4.3	4.3	2.8	3.3
2	4.03	4.2	4.3	5.6	6	9.6	8.8	9.2	6.1	7.9
3	7.23	7	7.2	9.1	10.6	16	15.2	15.6	1O.7	14.3
4	11.93	10.2	11.9	15.9	17.5	23.5	24.1	23.1	17.6	21.1
5	18.83	14.8	18.8	25.5	27.5	32.4	34.4	33.4	27.6	29.4
6	27.43	21.7	27.8	35.6	38.4	42.7	45.7	46.6	38.5	39.4
7	37.53	33	38.1	46.9	51.1	54	58.4	61	51.7	50.7
8	48.03	45.9	48.6	59	64.6	66.7	71.6	75.8	65.2	64.2
24	59.3	59.9	63.4	73.8	80.1	82.7	88.6	93.1	80.7	81.5

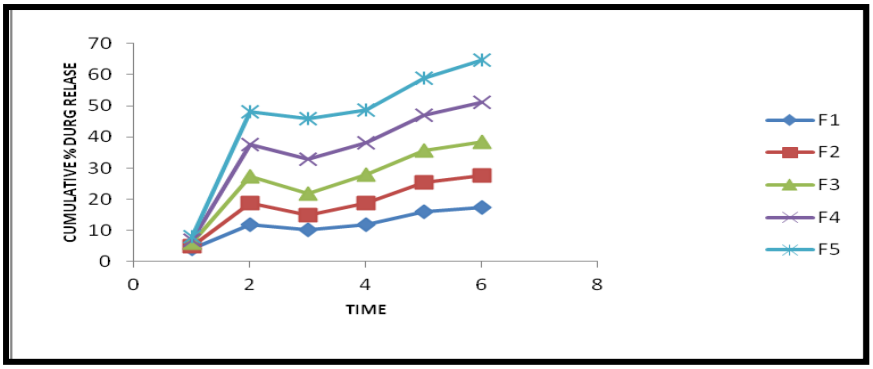

Figure.1.In-vitro permeation study of formulations F1 to F6

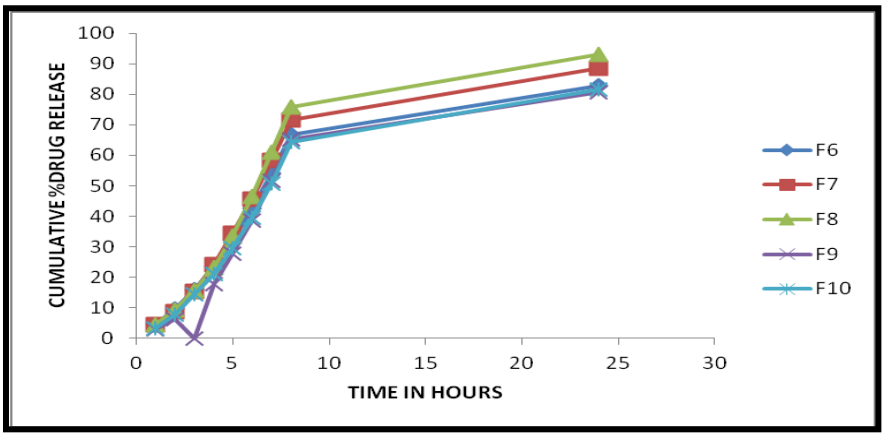

Figure.2. In-vitro permeation study of formulations F6 to F10

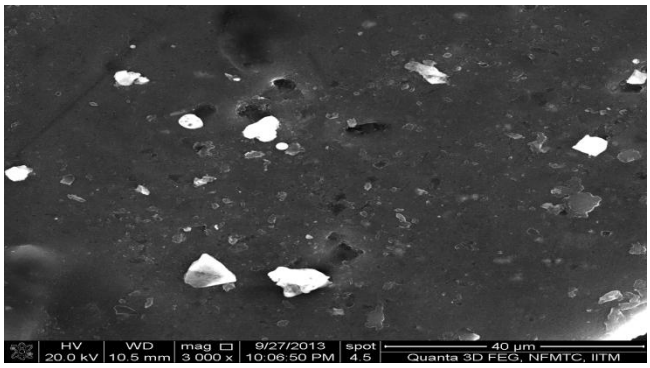

Figure.3. SEM Analysis For Optimized Formulation F8

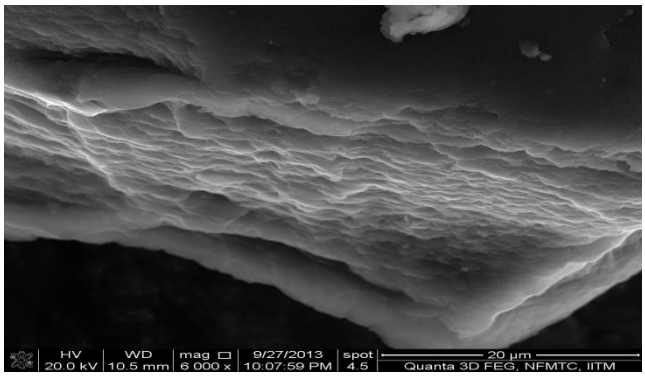

Figure.4.SEM Analysis For Optimized Formulation F8

CONCLUSION

From the in-vitro release results observed that the films prepared by using different ratios of HPMCK 15M,PVPK30 transdermal carvedilol patches were formulated using TWEEN 80 as a penetration enhancer proved to exhibit better release characteristics. It can be reasonably concluded that carvedilol can be formulated into transdermal patches to prolong its release characteristics. Thus the formulation HPMCK15M, PVPK30 (3: 2) F8 was found to be the best for controlled release in 93.1 % drug release in 24 hrs.

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