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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM OF PROPRANOLOL HYDROCHLORIDE

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ABSTRACT

The purpose of the work was an attempt to develop a transdermal drug delivery system of Propranolol using three different polymer combinations i.e. CAB-PVP in different ratios. Total of 7 patches were prepared out of which the CAB-PVP patches were found to have better characteristics than the other two patches. From the *in vitro* release results observed, it was noticed that patches prepared using CAB-PVP proved to exhibit better release characteristics. The better results for the physicochemical parameters of CAB- PVP patches. Based on the results it concludes that the formulation F7 Shows better In vitro dissolution release studies it concluded that the concentration of CAB:PVP at 3: 7 ratio shows better results for formulation of the propranolol transdermal patches.

KEYWORDS: Ttransdermal drug delivery, patches, in vitro dissolution.

INTRODUCTION

Transdermal drug delivery system is a means by which a pharmacologically active moiety may be continuously delivered systemically in an efficient, reliable and safe manner. They are capable of better performance than conventional delivery by monitoring the concentration, location and duration of drug action. Transdermal product has been in a significant upward trend and that is likely to continue for the foreseeable future.[3] The first adhesive transdermal delivery system (TDDS) patch was approved by the Food and Drug Administration in 1979 (scopolamine patch for motion sickness). Nitroglycerine patches were approved in 1981.[1-2] Transdermal clonidine was approved by the US Food and Drug Administration 1984 for the treatment mild-to-moderate hypertension alone or in combination with diuretic. This method of delivery became widely recognized when nicotine patches for smoking cessation were introduced in 1991. Over the past two decades, more than 35 transdermal products have been approved generating sales of $3.2billion in 2002, which is predicted to rise to $4.5billion in 2008. This rapid increase in the market value has lead to transdermal drug delivery becoming one of the fastest sectors within pharmaceutical industry. Historically medicated plaster can be viewed as the first development of transdermal drug delivery. It is designed to bring medication into close contact with skin so that drug can be delivered transdermally. The use of medicated plasters could be traced several 100 years back in ancient China. The medicated plaster has also been very popular in Japan and many are available as OTC pharmaceutical dosage forms, commonly called cataplasms. In United States the following three medicated plasters have been listed in official compendia namely belladonna plaster, mustard plaster and salicylic acid plaster. These plasters are rather simple in formulation and were developed mainly for local medication.[3]

Propranolol is a propanolamine that is propan-2-ol substituted by a propan-2-ylamino group at position 1 and a naphthalen-1-yloxy group at position 3. It has a role as a beta-adrenergic antagonist, an anxiolytic drug, an anti-arrhythmia drug, a vasodilator agent, an antihypertensive agent, a xenobiotic, an environmental contaminant and a human blood serum metabolite. It is a secondary amine, a propanolamine and a member of naphthalenes. It is functionally related to a 1-naphthol.[4]

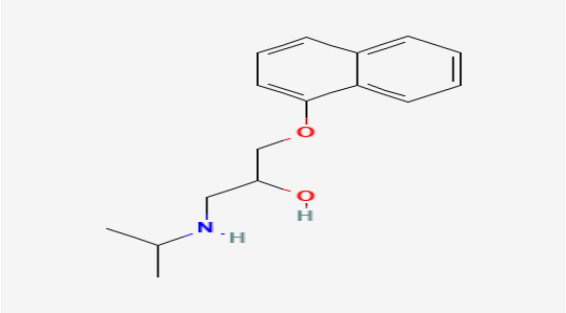

Figure1: Chemical structure of propranolol.

EXPERIMENTAL WORK[5-10]

MATERIALS AND METHODS:

Propranolol gift sample from AstraZeneca , Cellulose

acetate butyrate, Poly vinyl pyrrolidone ,Hydroxyl propyl methyl cellulose, Ethyl cellulose, Di n-butyl phthalate ,Isopropyl myristate, Potassium dihydrogen phosphate, Methanol, Chloroform, Ethanol Aluminium foil, Syringe 5 ml, Ammonia, Calcium chloride, Potassium chloride ,Cellulose membrane (0.2µ)

Methodology:

Standard graph of propranolol[44]

Preparation of stock solution

10 mg of Propranolol was dissolved in methanol and made upto 100 ml to obtain 100mcg/ml working standard.

Calibration graph of propranolol

Aliquots of 0.5 ml to 3.0 ml portions representing 5 to 30 mcg of drug were transferred to different 10 ml volumetric flask. To each flask methanol is added and made up to 10 ml. Then absorbance was measured at 314 nm against a blank solution prepared in similar manner without the addition of drug.

Development of patches

In the present study matrix type transdermal patches of Propranolol were prepared by mercury substrate method. A flat circular glass mould was fabricated for this purpose. The transdermal patches were prepared using polymers in different ratios. CAB and PVP patches were prepared by dissolving CAB in measured volume of chloroform and kept aside for 4 hours to facilitate the polymer to dissolve in the solvent. Then add specified quantities of PVP, DBP and isopropyl myristate as listed in table.5

A weighed amount of drug is dissolved in suitable solvent and dispersed in polymer mixture and this solvent is poured in to the ring placed on mercury surface in a Petri dish and solvent evaporation was controlled by covering with a funnel. After 24 hours the patches were removed and kept in dessicator to remove any adhering solvents, the films were cut in circular disc with 3.8cm diameter. These patches were wrapped in aluminium foil, packed in self-sealing cover and kept in dessicator.

Table 5: Composition of transdermal patches.

Formulation	MT in mg	CAB in parts	PVP in parts	DBP in % W/W	IPM in % W/W
F_1	15	4.5	0.5	30	20
F_2	15	4.0	1.0	30	20
F_3	15	3.5	1.5	30	20
F_4	15	3.0	2.0	30	20
F_5	15	2.5	2.5	30	20
F_6	15	2.0	3.0	30	20
F_7	15	1.5	3.5	30	20

Evaluation of transdermal patches[11-16]

The prepared patches were evaluated for their physico-chemical parameters, *in vitro* diffusion studies, skin irritation and stability studies.

Physicochemical parameters

1. Weight variation

As weight variation between the formulated patches can lead to difference in drug content and *in vitro* behaviour, a study was carried out weighing 5 patches in an electronic balance. The average weight of a patch and its standard deviation was calculated by using the following formulae.

Average weight of each patches = total weight of 5 patches/5

2. Percentage of moisture content

The films were weighed individually and kept in a dessicator containing anhydrous calcium chloride at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to the final weight.

3. Percentage moisture uptake

Moisture uptake can influence the mechanical strength and drug release of the transdermal therapeutic system. It was done by weighing the film and keeping in a dessicator at room temperature for 24 hours and patches were removed and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a dessicator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as difference between final weight and initial weight with respect to final weight.

4. Drug content

A film was cut into small pieces, put into a 100ml buffer (PH- 7.4) and shaken continuously for 24 hours. Then the solution was filtered. After filtration, the drug content was estimated at wave length 314nm.

5. Film thickness

The thickness was measured at 5 different places for 5 films using a dial caliper and mean value were calculated.

6. Tensile strength

It was determined by using a modified pulley system. Weight was gradually increased so as to increase the

pulley force till the patch broke. The percentage elongation before the patch broke was noted with the help of a magnifying glass on a graph paper and the tensile strength was calculated as kg/mm^2.

***In vitro* permeation studies**

In vitro permeation studies were performed using Franz diffusion cell. It consists of a donor compartment and a receptor compartment. The cellulose membrane[45] was mounted between the donor compartment and receptor compartment of the diffusion cell. The formulated patches were placed over the membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 37 ± 1^{0}C. The samples were withdrawn at different time intervals and analysed for drug content. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative amount of drug permeated/cm^2 of patches were plotted against time.

RESULTS AND DISCUSSION

Compatibility studies IR

The presence of all characteristic peaks of Propranolol, in IR spectra obtained with Propranolol and the other excipients confirms the intactness of the drug in the polymer matrix.

UV Spectrum:

The propranolol shows Absorbance maximum at 314 nm

Table 4: Data of absorbances of standard graph.

Sl. No.	Concentration in mcg/ml	Absorbance at 314 nm
1	5	0.114
2	10	0.221
3	15	0.31
4	20	0.405
5	25	0.499
6	30	0.591

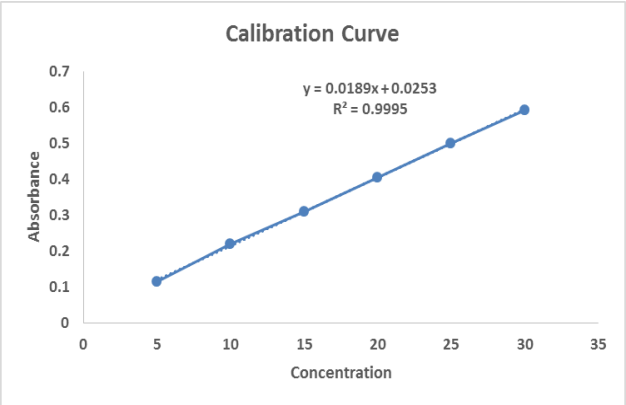

Figure 2: Calibration curve of propranolol.

Formulation and *In vitro* evaluation

Total 7 patches were prepared. (F_1 – F_7) contained the polymers CAB & PVP. All the 7 patches were evaluated for physical appearance, moisture content, moisture uptake, weight variation, drug content, thickness and tensile strength. The values are represented in table 6, 7 and 8.

Physical appearance

The physical appearance for the patches F_1-F_7 was found to be transparent, smooth and flexible.

Moisture Content & Moisture uptake

All the patches (F_1- F_7) the percentage moisture content and moisture uptake was found to increase with increase in the PVP concentration.

Weight variation

The results were tabulated

Drug content

Drug content in all the batches were found to be similar with minor variations. The CAB- PVP patch showed maximum drug content.

Film thickness

Out of 7 patches; formulations containing results were tabulated

Tensile strength

The tensile Strength of containing results were tabulated.

Table 6: Physico–chemical properties of the prepared transdermal patches of Propranolol Hydro chloride.

Patch no	Physical appearance	Percentage Moisture content(±SD)	Percentage Moisture uptake (±SD)	Weight variation in mg (±SD)	Drug content in mg(±SD)	Film thickness in µg/cm2 (±SD)	Tensile Strength in kg/ mm2
F1	Transparent, flexible and smooth	4.94±2.18	5.06±3.77	107.43±0.78	0.9838±0.8	0.138±1.44	1.81±3.27
F2	Transparent, flexible and smooth	5.39 ±2.71	6.65 ±5.14	110.62±0.33	0.9846±1.7	0.136±1.36	1.76±2.65
F3	Transparent, flexible and smooth	7.21 ±3.22	7.85 ±4.27	114.21±0.39	0.9896±0.6	0.132±2.24	1.28±3.69
F4	Transparent, flexible and smooth	8.52±3.81	8.74 ±2.84	117.33±0.72	1.0022±0.36	0.141±1.28	1.42±4.15
F5	Transparent, flexible and smooth	9.14 ±3.64	9.79 ±3.91	122.57±0.68	1.0080±1.1	0.135±2.12	1.69±2.41
F6	Transparent, flexible and smooth	9.52±5.24	10.23±4.81	124.12±0.82	1.018±0.22	0.138±1.45	1.34±1.15
F7	Transparent, flexible and smooth	10.11 ±5.19	11.47 ±3.21	127.45±0.42	1.030±0.52	0.134±1.54	1.53±2.67

n=5

***In vitro* release**

Formulations F_1.F_7 containing CAB-PVP in the ratios 9:1,8:2,7:3, 6:4, 5:5, 4:6 and 3:7 showed a steady increase in the release with increase in time. The cumulative release of Propranolol released from polymeric films in 24 hours was found to be between 42.9% to 49.2%.

Table 9: Cumulative percentage released for the patches F_1 to F_7.

Time	F1CAB-PVP 9:1		F2 CAB-PVP 8:2		F3CAB-PVP 7:3		F4CAB-PVP 6:4		F5CAB-PVP 5:5		F6CAB-PVP 4:6		F7CAB-PVP 3:7	
	Cumulative amount released µg/cm2(±SD)	Cumulative % released	Cumulative amount released µg/cm2 (±SD)	Cumulative % released	Cumulative amount released µg/cm2 (±SD)	Cumulative % released	Cumulative amount released µg/cm2 (±SD)	Cumulative % released	Cumulative amount released µg/cm2 (±SD)	Cumulative % released	Cumulative amount released µg/cm2 (±SD)	Cumulative % released	Cumulative amount released µg/cm2 (±SD)	Cumulative % released
1	15.61±3.64	1.586	17.99±2.76	1.82	20.07±5.14	2.028	22.78±3.94	2.272	23.34±4.76	2.315	26.61±5.73	2.613	27.73±2.67	2.692
2	44.33±2.46	4.505	48.42±3.28	4.917	51.24±2.75	5.177	57.44±2.76	5.73	61.76±2.25	6.12	64.56±4.44	6.34	67.37±4.94	6.540
3	74.27±2.95	7.549	78.71±4.13	8.0	81.37±4.37	8.222	85.22±5.34	8.504	91.74±3.66	9.101	95.54±3.49	9.385	97.39±2.48	9.455
4	91.57±5.23	9.307	92.37±2.17	9.389	96.27±3.92	9.728	102.68±4.78	10.24	109.04±5.16	10.81	114.14±2.31	11.212	121.42±3.26	11.788
5	117.61±4.35	11.95	122.46±5.32	12.447	129.54±5.78	13.090	133.76±2.61	13.34	138.42±4.63	13.73	143.91±3.97	14.136	147.39±4.44	14.369
6	142.13±3.27	14.44	148.61±4.74	15.093	156.32±3.46	15.79	161.11±4.64	16.07	166.95±4.58	16.56	173.32±4.59	17.025	178.61±3.53	17.340
7	161.87±4.48	16.45	180.06±3.92	18.28	183.24±4.17	18.516	188.97±3.43	18.85	193.31±2.97	19.17	200.07±3.27	19.65	201.09±3.14	20.105
8	183.38±3.18	18.639	197.21±2.62	20.02	202.57±2.55	20.46	210.05±5.67	20.96	216.77±3.72	21.50	225.46±2.95	22.147	229.59±5.61	22.290

9	199.78±4.13	20.306	208.72±5.87	21.198	214.62±3.42	21.687	221.70±2.82	22.12	226.51±5.69	22.47	249.76±4.66	24.534	253.39±3.85	24.600
10	211.62±4.77	21.510	224.42±3.41	22.79	236.47±4.68	23.89	241.28±5.37	24.07	248.52±2.18	24.65	273.39±2.74	26.85	281.42±5.39	27.322
24	441.32±2.95	44.85	451.88±2.82	45.89	463.97±2.64	46.884	465.37±4.11	46.444	477.25±2.89	47.34	486.22±4.81	47.76	507.39±4.74	49.26

SUMMARY AND CONCLUSION

The purpose of the work was an attempt to develop a transdermal drug delivery system of Propranolol using three different polymer combinations i.e. CAB-PVP in different ratios. Total of 7 patches were prepared out of which the CAB-PVP patches were found to have better characteristics than the other two patches.

The compatibility studies confirmed the absence of chemical interaction between the drug and other excipients employed in the formulation. They have been evaluated for physicochemical parameters like physical appearance, average weight, thickness, percent moisture content, percent moisture uptake and drug content. Release rates were found out by *in vitro* diffusion studies using Franz diffusion cell.

From the *in vitro* release results observed, it was noticed that patches prepared using CAB-PVP proved to exhibit better release characteristics. The results for the physicochemical parameters of CAB- PVP patches. Based on the results it concludes that the formulation F7 Shows better In vitro dissolution release studies it concluded that the concentration of CAB: PVP at 3: 7 ratio shows better results.

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