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Design and Development of Transdermal Therapeutic System of Carvedilol Using Combination of Natural and Synthetic Polymers

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ABSTRACT

The present study was mainly focused on investigating the influence of concentration and combination of HPMC K4M, Carbopol 934P and Chitosan on physical characterization and drug release behavior of carvedilol transdermal films prepared by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by differential scanning calorimetry and infrared spectroscopy. The results suggested no physicochemical incompatibility between the drug and the polymers. The prepared films were evaluated for physicochemical characteristics like weight variation, thickness, folding endurance, tensile strength, percentage moisture uptake, water vapor transmission rate, percentage flatness and in vitro permeation study. In vitro permeation studies were performed by using Franz diffusion cells. The drug release profiles of selected formulations were subjected to kinetic treatment using zero order, first order, Higuchi and korsmeyer's peppas kinetic models. The results followed Higuchi kinetics (r^2=0.951−0.995) and the mechanism of release was diffusion mediated. Based on physicochemical and in vitro permeation studies, transdermal film prepared by combination of HPMC K4M and Chitosan with ratio 3:1 selected as optimized formulation shows the drug release more than 24 hours with good flexibility and stability at 25^{0}C. The developed transdermal film increases the efficacy of carvedilol for the treatment of hypertension.

KEYWORDS

Transdermal, carvedilol, Optimization, Carbopol934P, Chitosan, HPMCK4M, differential scanning calorimetry, Fourier transfer infrared spectroscopy

INTRODUCTION

Carvedilol is used for the treatment of mild to moderate hypertension.[1] Carvedilol reduce the blood pressure by blocking β1 and α1 adrenergic receptors.[2] Carvedilol possess antioxidant activity and antiproliferative effect on vascular smooth muscle cells thus it provide major cardiovascular protection and used in the treatment of coronary artery disease and congestive heart failure.[2]

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The drug is reported to be 23% poor oral bioavailability with significant first pass hepatic metabolism.[3] Its short biological half life 6 hrs needs frequent administration. To avoid invasive drug therapy such as injection and frequent dosing regimen for maintaining drug blood level for an extended period of time, an alternative non-oral delivery system has been studied to provide controlled release of drug for prolonged period.[4]

Transdermal drug delivery system (TDDS) bypassing first pass metabolism, reducing frequency of administration, potentially decreasing side effects, improved patient

compliance sustaining drug delivery and interruption or termination of treatment when necessary.[5,6] Carvedilol possesses ideal characteristics that a drug must have for formulating a transdermal drug delivery system: low molecular mass (406.5), high lipid solubility (log octanol/buffer pH 7.4: 0.61±0.06), short plasma half-life, poor oral bioavailability effective in low plasma concentration as well as high degree of first pass metabolism.[7] Therefore transdermal route is an alternative for administration of carvedilol.

Various drug delivery systems are reported in which Carbopol 934P, Chitosan and HPMCK4M are used as polymer to control the drug release from the delivery system.[8-10] In the present study transdermal films were prepared by combination of these polymers are neither extremely hydrophobic nor hydrophilic and therefore, provides controlled drug release characteristics.

In the present work an attempt was made to optimize the physicochemical properties and in vitro drug permeation pattern of drug from matrix type transdermal films using different combinations of chitosan with Carbopol 934P and HPMCK4M and control the drug release for prolong period of time and thereby improving the therapy of carvedilol for hypertension.

MATERIALS AND METHODS

MATERIALS

Carvedilol was received as a gift sample from Sun Pharmaceutical Ltd. (Baroda, India). Chitosan was supplied by fisheries technology institute (cochine India). Carbopol 934P was purchased by corel pharma Pvt Ltd. (India). HPMC K4M and propylene glycol were purchased from Loba Chemie Ltd. (India). All the other chemicals were of analytical grade.

INVESTIGATION OF PHYSICO-CHEMICAL COMPATIBILITY OF DRUG AND POLYMER

The physicochemical compatibility between drug and polymers were studied by differential scanning calorimetry (DSC) and fourier transform infrared (FTIR) spectroscopy. In DSC (Perkin-Elmer–Pyris 6 DSC, Salem, MA) analysis, the samples were weighed (5 mg), hermetically sealed in flat-bottom aluminum pans, and heated over a temperature range of 50 to 25^0C in an atmosphere of nitrogen (20 ml/min) at a constant increasing rate of 10^0C/min. The infrared (IR) spectra were recorded using an FTIR spectrophotometer (FTIP-800, Biorad, Munich, Germany) by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}.

METHOD OF PREPARATION OF TRANSDERMAL FILMS

FABRICATION OF BLANK FILMS

Transdermal films were prepared by solvent casting method. The blank films were prepared by different concentration (2%, 2.5% and 3%) of different polymers, HPMC K4M, Carbopol 934P and Chitosan. Solution of Chitosan was prepared by dissolving in 1.0% w/v acetic acid solution and solution of HPMC K4M and Carbopol 934P were prepared in water: ethanol mixture (1:1). The above solution (12 ml) was poured into a glass bangle (25.5 cm^2) placed over the mercury filled petridish and kept in an oven at 40° for complete drying. Films produced by chitosan were washing with 50% v/v ethanol to remove surface bound traces of acid. The dried films were removed from the glass bangle and stored in desiccators until use (Table 1).

FABRICATION OF DRUG LOADED FILMS

Add 10%, 20% w/w, 30% w/w (with respect to dry weight of polymer) of propylene glycol (PG) followed by 2.6% w/w (with respect to dry weight of polymer) of carvedilol to Polymeric solutions prepared for blank film and stirred for 30 min (Table 3). Drug containing polymeric solution (12 ml) were poured into a glass bangle (25.5 cm^2) placed over the mercury filled petridish and kept in an oven at 40° for complete drying. Films produced were washed with 50% ethanol to remove surface bound

traces of acid. The dried films were removed from the petridish and stored in a desiccator until use.

Table: 1 Composition of transdermal film using combination of polymers

Batch code	HPMC : Chitosan (2%w/v)	CB-934P : Chitosan (2%w/v)
HCS1	25 : 75	
HCS2	50 : 50	
HCS3	75 : 25	
CBCS1		25 : 75
CBCS2		50 : 50
CBCS3		75 : 25

All the batches containing 20%w/w propylene glycol and 2.6%w/w Carvedilol.

EVALUATION OF PHYSICOCHEMICAL PROPERTIES OF TRANSDERMAL FILMS[11-14]

Weight Variation

Weight variation was studied by individually weighing three randomly selected patches. Such determination was performed for each formulation.

Drug Content

A 1-cm^2 film was cut into small pieces, put into a 100-ml phosphate buffer pH 7.4, propylene glycol and methanol (45:15:40) buffer and shaken continuously for 24 hours. Then the whole solution was ultrasonicated for 15 minutes. After filtration, the drug content was estimated using simadzu 1700 UV-Vis double beam spectrophotometer at 285 nm.

Thickness

Patch thickness was measured using digital screw gauze (Mitutoyo, Japan) at three different places and the mean value was calculated.

Flatness

Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

Folding Endurance

Folding endurance was determined by repeatedly folding the film (2 x 2 cm^2) at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value.

Tensile Strength

Tensile strength was measured using modified analytical two pan balanced method. The patch of 2 cm width and 5 cm length was cut and clamped between 2 clamps, on one side weights are added to the pan until the patch breaks. The weight required for breaking the patch was taken as the measure tensile strength of a patch.

Percentage of Moisture Uptake

A weighed film kept in a desiccator at room temperature for 24 hours was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Water vapour transmission rate (WVTR)

Glass vials of equal diameter were used as transmission cells. Approximately 1 gm fused calcium chloride was taken in the cells and film of area equivalent to brim of vial (1.36 cm^2) was fixed with the help of an adhesive. Then all the cells were weighed accurately and kept in an accurate saturated solution of aluminum chloride. The humidity was found to be 84% RH. The cells are taken out and weighed after 24 hrs of storage.

IN VITRO PERMEATION STUDY

In vitro permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22ml. Cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated films were placed over the membrane and covered with paraffin film. 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 beads at 50 rpm, the temperature was maintained at 32±0.5°C. The samples were withdraw at different time intervals and analyzed for drug content specrtophotometrically. The fluid in receptor compartment was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.

KINETIC MODELING AND MECHANISM OF DRUG RELEASE

The dissolution profiles of different batches prepared by combination of polymers with different ratio were treated with zero order, first order, Higuchi, Korsemayer and peppas equations to understand the release mechanism.[15-17]

STABILITY STUDIES OF OPTIMIZED FORMULATION

The optimized formulation was exposed to ambient temperature (25°±0.5^{0}C) and at elevated temperature (45°±0.5^{0}C). Transdermal films with an area of 25 cm^2 were kept in an oven for four weeks. The film sample with an area of 1 cm^2 was cut from each formulation, and it was analysed for drug content at the end of every week.

RESULT AND DISCUSSION

INVESTIGATION OF PHYSICO-CHEMICAL COMPATIBILITY OF DRUG AND POLYMERS

The DSC analysis of the pure carvedilol showed a sharp endothermal peak at 118.14^{0}C, corresponding to the melting point of drug (Fig.1.a). The DSC analysis of the physical mixtures of the drug and polymers revealed that there was insignificant change in melting point of carvedilol (Fig.1.b, 1.c, 1.d). The DSC results suggest that the drug and polymers are compatible.

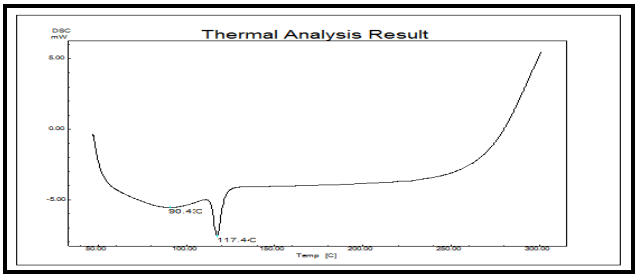

Figure: 1.a. DSC spectra of carvedilol

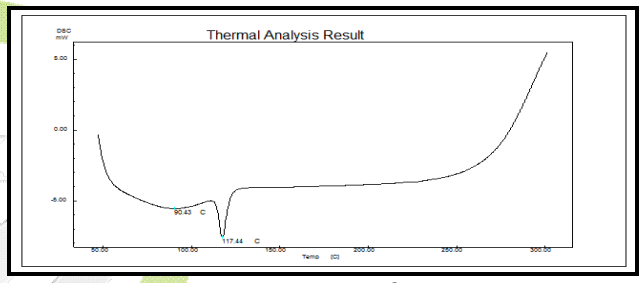

Figure: 1.b. DSC spectra of Carvedilol and Chitosan

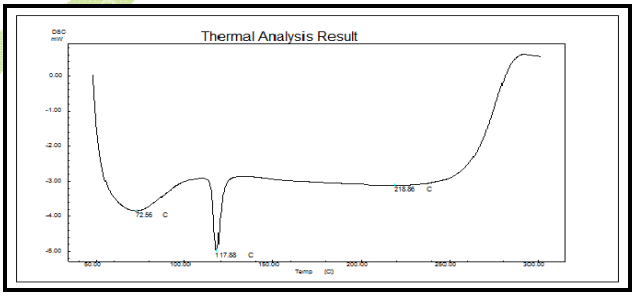

Figure: 1.c. DSC spectra of Carvedilol and HPMC

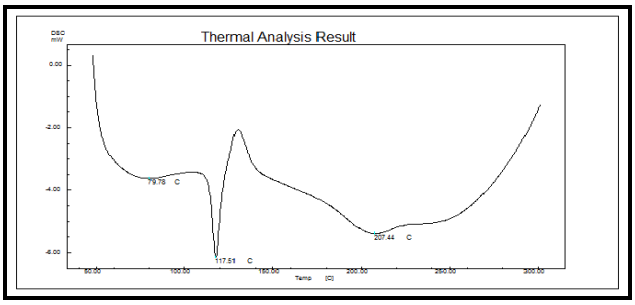

Figure: 1.d. DSC spectra of Carvedilol and Carbopol 934P

The IR spectral analysis of carvedilol alone showed that the principle peaks were observed at wave numbers 3348, 1630, 1503, 980 and 958 cm^{-1}, confirming the purity of drug (Fig. 2.a). In the IR spectra of physical mixture of carvedilol and polymers revealed that there was no significant change in wave numbers of major peaks of carvedilol (Fig. 2.b, 2.c, 2.d). The FTIR results suggest that the drug and polymers are compatible.

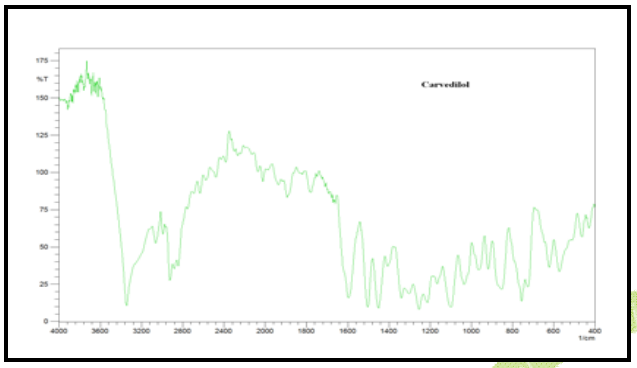

Figure: 2.a. FTIR spectra of carvedilol

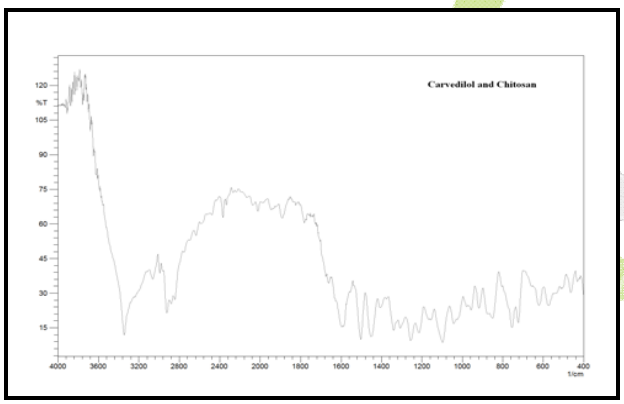

Figure: 2.b. FTIR spectra of Carvedilol and Chitosan

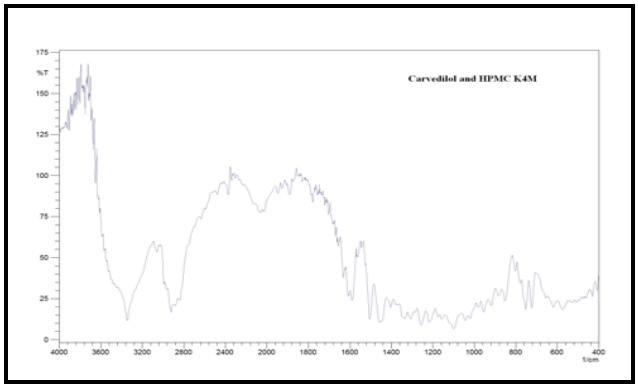

Figure: 2.c. FTIR spectra of Carvedilol and HPMC K4M

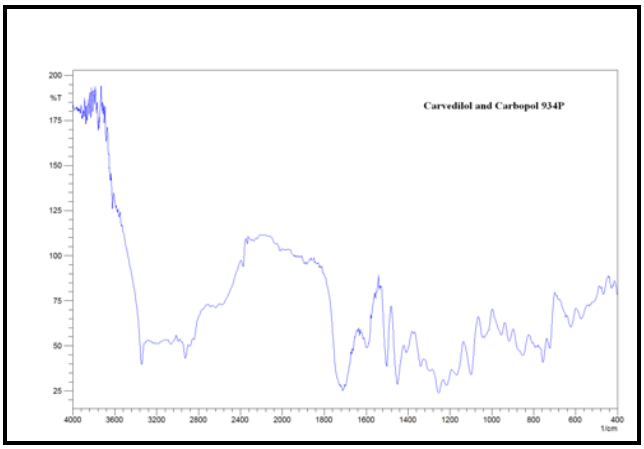

Figure: 2.d FTIR spectra of Carvedilol and Carbopol 934P

OPTIMIZATION OF POLYMER CONCENTRATION IN BLANK FILMS

Physicochemical characterization of patches

The results of physicochemical characterization of nine blank films are shown in Table 2. All the prepared films were smooth in surface. The weights of film were increase with increase concentration of polymer. The film with 2% concentration of polymer shows minimum deviation. All the formulations were measured thickness with low standard deviation values ensure the uniformity of films prepared by solvent casting method. The percentage flatness of all blank films ranged from 98.4% to 100% which indicate all films were flat in surface. Batch H1 and CB1 show 100% flatness. The folding endurance of blank films was poor (11-46). The folding endurance value decreases with increases the concentration of polymers. The tensile strength of blank films was also poor (21-31 gm/10 cm^2).

The result of folding endurance and tensile strength shows that the films were not flexible. The moisture uptake study shows, the moisture uptake increases with increases the concentration of hydrophilic polymers but the low moisture uptake could protect the formulations from microbial contamination and reduce bulkiness of films. All the films were permeable to water vapor. Water vapor transmission rate were decreases with increase the concentration of polymers.

The results suggest that the 2% concentration for all the polymers gave the satisfactory result but films were hard and brittle and it required proper concentration of plasticizer.

endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

Table: 2 Physicochemical characteristics of blank formulations.

Batch Code	Conc (%)	Weight (mg)	Average thickness (mm)	Folding endurace	% F	Tensile strength (gm/10cm^2)	% MU (g/cm^2. day)	WVTR (g/cm^2. day)
CS1	2	243.34±0.21	0.154±0.022	16±2.68	99.7	22±0.32	5.15	0.0232
CS2	2.5	304.27±0.36	0.166±0.016	12±2.26	98.9	25±0.21	7.64	0.0186
CS3	3	363.9.±0.31	0.186±0.021	11±1.37	99.6	27±0.28	8.64	0.0079
H1	2	246.14±0.28	0.143±0.042	46±2.80	100	21±0.25	7.52	0.0289
H2	2.5	309.45±0.45	0.154±0.027	21±1.65	98.4	26±0.26	11.15	0.0204
H3	3	368.64±0.48	0.168±0.028	21±0.84	98.6	28±0.36	12.94	0.0106
CB1	2	245.65±0.24	0.152±0.021	19±2.45	100	24±0.21	8.84	0.0239
CB2	2.5	309.71±0.40	0.168±0.036	18±0.81	99.1	28±0.47	12.91	0.0196
CB3	3	308.25±0.37	0.183±0.041	16± 1.78	98.5	31±0.28	14.26	0.094

All values are expressed as mean ± SD (n=3), Cs indicates chitosan; H, HPMC K4M; CB, Carbopol 934P: F. Flatness.

OPTIMIZATION OF PLASTICIZER CONCENTRATION

The films containing 2% concentration of different polymers were plasticized with different concentration of propylene glycol (10%, 20% and 30% w/v) as plasticizer and loaded with 2.6%w/v of carvedilol and evaluate for physical characterization (Table 3) and in vitro drug release study. Plasticized films were smooth, uniform and free from wrinkles and were easy to handle compared to non plasticized film. Good uniformity of drug content among the batches were observed with all patches and ranged from 98.38 to 99.84. A folding endurance test was carried out to check the strength and flexibility of films and the effectiveness of the plasticizer. The folding endurance value were increases with increases the concentration of plasticizer. Folding

The tensile strength has linear correlation with increase in concentration of plasticizer. WVTR study results indicated that hydrophilic plasticizer (PG) were responsible for the higher WVTR. All the films were permeable to water vapour. The percentage moisture uptake increases with increases the concentration of propylene glycol. The increase in moisture uptake attributed the hygroscopic nature of polymer- glycerol composite film.

In vitro drug release study

Propylene glycol is not only plasticizer but also permeation enhancer so it affects the drug release rate from the films. The drug release rate was increased in plasticized films than blank films. 10% propylene glycol shows less release rate compared to 20% and 30%, but there was no much difference between 20% and 30% propylene glycol concentration so 20% of PG

was helped as ideal concentration. The release pattern was found to be in order of Chitosan> Carbopol 934P> HPMC K4M. The drug release profile depict that drug release was faster in case of chitosan than HPMC and Carbopol. So to get the desired release profile, combination of polymers Chitosan with HPMCK4M and Carbopol 934P were further studied.

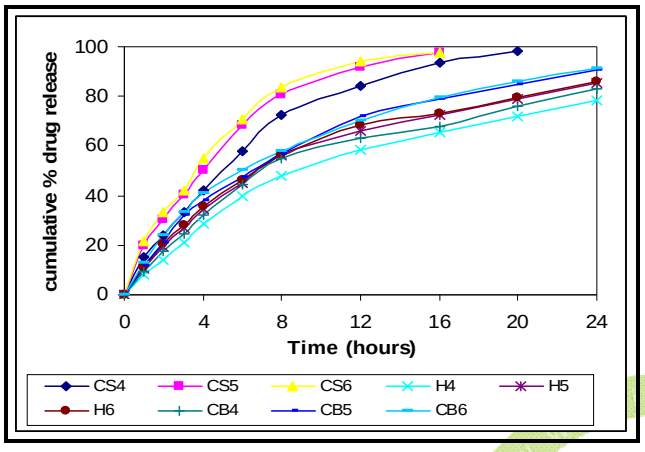

Figure: 3 Drug release profile of formulations containing different concentration of propylene glycol with 2% polymeric film.

EFFECT OF COMBINATION OF POLYMERS WITH DIFFERENT CONCENTRATION

To check the effect of chitosan on drug release from HPMC and CB934P, combination of polymers with different ratio were selected (Table 1). The result of physicochemical parameters depict that all the prepared films were uniform in thickness, flexible and smooth in surface.

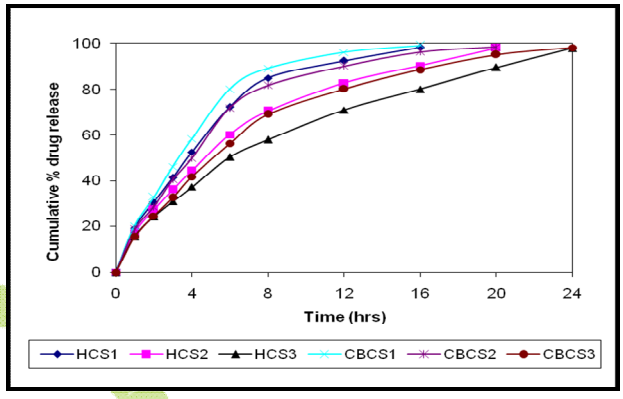

Figure: 4 In vitro drug release profile of formulations containing different polymers combinations.

Table: 3 Physicochemical characteristics of drug loaded formulations.

Batch Code	Conc of PG (%)	Weight (mg)	Average thickness (mm)	Folding endurace	% F	Tensile strength (gm/10cm^2)	% MU (g/cm^2. Day)	WVTR (g/cm^2. day)
CS4	10	247.34±0.21	0.155±0.022	88±1.72	99.7	41.47±0.21	6.17	0.0293
CS5	20	250.27±0.36	0.156±0.016	142±2.88	99.1	65.26±0.28	8.14	0.0326
CS6	30	254.09±0.41	0.156±0.042	158±4.03	98.8	70.82±0.10	11.60	0.0389
H4	10	246.14±0.28	0.144±0.042	112±4.28	100	46.27±0.26	7.92	0.0328
H5	20	248.45±0.45	0.144±0.027	154±5.21	98.6	78.42±0.36	9.15	0.0374
H6	30	251.64±0.48	0.145±0.028	178±7.18	98.6	80.21±0.27	12.04	0.0406
CB4	10	245.65±0.24	0.152±0.031	78±1.78	99.4	46.86±0.47	9.12	0.0301
CB5	20	247.71±0.40	0.153±0.046	138±4.35	100	68.02±0.28	10.98	0.0346
CB6	30	250.25±0.37	0.153±0.041	156±3.93	98.6	75.58±0.52	12.60	0.0384

All values are expressed as mean ± SD (n=3), All the batches containing 2.6%w/w Carvedilol Cs indicates Chitosan; H, HPMC K4M; CB, Carbopol 934P; F, Flatness.

Batch HCS3 showed highest tensile strength (91.45 gm/10cm^2) and lowest thickness (0.148 mm). Among all the batches HCS3 have highest water vapour transmission rate (0.0287 g/cm^2.day).

released from the film occurs by Non- fickian type of diffusion. Overall results of kinetic modeling suggest that diffusion is dominant mechanism for drug release following Non-Fickian type of diffusion (Table 5).

Table: 4 Physicochemical characteristics of films containing different polymers combinations.

Batch Code	Weight (mg)	Average thickness (mm)	Folding endurace	% F	Tensile strength (gm/10cm^2)	% MU (g/cm^2. day)	WVTR (g/cm^2.day)
HCS1	248.31±0.41	0.151±0.023	156±4.68	100	78.26±0.32	8.76	0.0233
HCS2	249.07±0.38	0.150±0.031	162±2.26	98.9	86.13±0.21	9.05	0.0261
HCS3	249.19±0.21	0.148±0.016	171±5.37	99.6	91.45±0.28	9.94	0.0287
CBCS1	249.14±0.64	0.156±0.024	136±2.80	100		9.33	0.0202
CBCS2	249.45±0.35	0.156±0.044	136±3.65	99.4	74.05±0.26	10.52	0.0237
CBCS3	248.64±0.21	0.155±0.037	121±2.84	98.6	81.73±0.36	12.15	0.0243

All values are expressed as mean ± SD (n=3), All the batches containing 2.6%w/w Carvedilol, F indicate Flatness.

IN-VITRO DRUG RELEASE STUDY

The results of in vitro drug release depict that combination of chitosan with HPMC and carbopol 934P increase the drug release rate than films prepared with HPMC and carbopol 934P alone. Among all prepared formulation, HCS3 would be a better formulation based on in vitro drug release study it release the drug in sustained release pattern 24hours without significantly releasing the drug in burst manner in initial hours.

KINETIC TREATMENT OF DISSOLUTION PROFILES

The result of kinetic modeling shows that drug release appears to fit the Higuchi model suggesting release occurs by diffusion mechanism. The data were subjected to Korsmayer's- peppas equation, the lines obtained were linear (R^2= 0.948 to 0.992) and the release exponent 'n' value vary between 0.581 to 0.622, which explained that drug

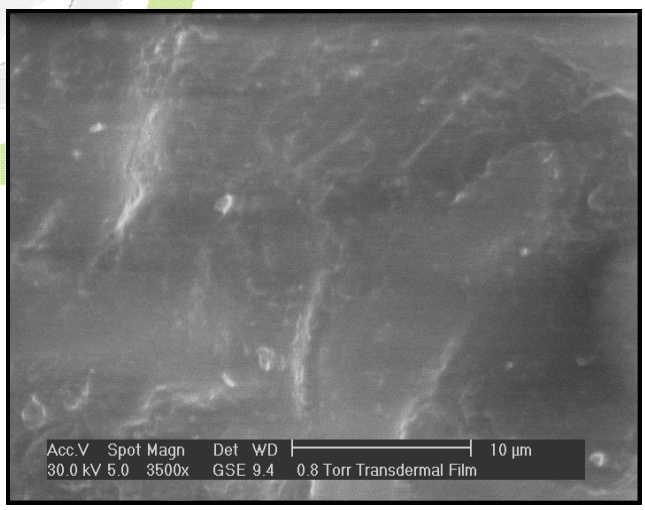

Figure: 5 SEM photograph of HCS3 formulation

STABILITY STUDIES

Stability studies of optimized formulation (HCS3) were carried out at 25°C and 45°C for four weeks. There was no change in physical characteristics of film. It was observed that the

Table: 5 Result of model fitting of batches prepared by combination of polymers with different ratio.

Formulation code	Zero order equation		First order equation		Higuchi's equation	Korsmeyer's peppas Equation	
	K	R^2	K	R^2	R^2	R^2	n
HCS1	3.75	0.924	0.067	0.802	0.995	0.992	0.581
HCS2	4.59	0.886	0.078	0.759	0.985	0.982	0.597
HCS3	5.95	0.853	0.094	0.735	0.966	0.969	0.622
CBCS1	3.90	0.873	0.067	0.734	0.977	0.974	0.603
CBCS2	4.67	0.814	0.074	0.689	0.951	0.952	0.585
CBCS3	5.98	0.809	0.090	0.684	0.949	0.948	0.605

percentage drug remaining was slightly affected by temperature (Fig. 6). The result of stability study suggested that the prepared films were more stable at 25^0C.

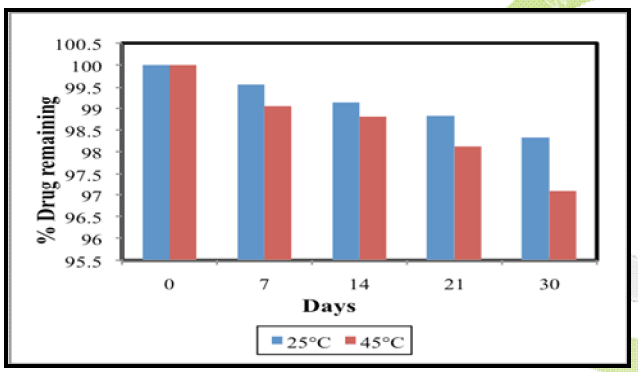

Figure: 6 Stability study of best batch for percentage drug retention at different temperatures for 30 days.

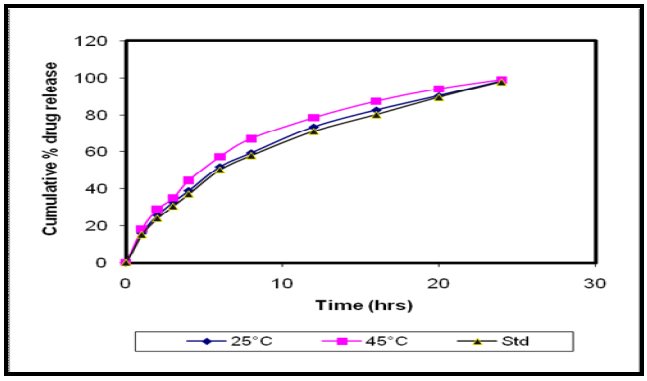

Figure: 7 Stability study of best batch for percentage drug release at different temperature after 30 days.

CONCLUSION

The transdermal films of carvedilol could be successfully prepared using HPMC K4M and Chitosan (3:1) with propylene glycol as a plasticizer. The prepared transdermal patches extended the release of carvedilol for 24 h without significantly releasing the drug in a burst manner and thereby it improves the therapy of hypertension. However *in-vivo* study is further necessary to confirm therapeutic efficacy of formulation.

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REFERENCES

1. Alfred Goodman Gilman, "The pharmacological basis of therapeutics", 11th edition, New York, Laurence B., John L. and Keith P., 1805.
2. Molendroff E., Reiff K. and Neugebauer G., "Pharmacokinetics and bioavailability of carvedilol a vasodilating beta blocker" Eur J Pharm, 1987, 33, 511-513.
3. Nemergut G., "Review of carvedilol in extended release formulation, Pharmacotherapy perspective", 2007, 5, 46-49.

4. Ubaidolla U., Reddy M., Ruckmani K. and Ahmad F., "Transdermal therapeutic system of carvedilol: effect of hydrophilic and matrix on in vitro and in vivo characteristics", AAPS Pharm Sci Tech, 2007, 8(1), 118-122.
5. Ryan D.G. and Tim A.P., "Transdermal drug delivery technology", www.drug delivery technology.com.
6. Chien Y., "Transdermal therapeutic system". In: Robinson J. and LEE A., Controlled drug delivery fundamentals and applications. 2nd ed., Newyork, NY: Marcel Dekker, 1987, 524-552.
7. Shivhare U., Dorlicker V., Bhusari K. and Mathur V., "Effect of polymeric composition s on pharmacotechnical properties of carvedilol transdermal film" Int J Pharm sci and Nanotech, 2009, 2(1), 118-122.
8. Jain N.K., "Controlled and novel drug delivery", first edition, CBS publishers and distributers, New Delhi.1997.
9. Whid A. Sridhar B. and Shivkumar S., "Preparation and evaluation of transdermal delivery system of etoricoxib using modified chitosan", Ind J Pharm Sci, 2008, 4, 455-460.
10. Vamsi V., Ramesh G., Chandrashekhar K. and Rao M., "Development and in vitro evaluation of buccoadhesive carvedilol tablets" Acta Pharm. 2007, 57, 185-197.
11. Jamakandi A., Mulla J. and Vinay b., "Formulation, characterization and evaluation of matrix type transdermal patches of a model antihypertensive drug", Asian J Pharm, 2009, 1, 59-65.
12. Alam M., Baboota S. and Kohli K., "Development and evaluation of transdermal patches of celecoxib", PDA J Pharm Sci Technol, 2009, 63(5), 429-437.
13. Shinde A., Garala k. and More H., "Development and characterization of transdermal therapeutics system of tramoldol hydrochloride", Asian J Pharm, 2008, 6(1), 265-269.
14. Limpongsa E. and Umprayn K., "Preparation and evaluation of diltiazem hydrochloride diffusion-controlled transdermal delivery system", AAPS Pharm Sci Tech, 2008, 9(2), 464-470.
15. Higuchi T., "Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices". J Pharm Sci, 1963, 52, 1145-57.
16. Donbrow M. and Samuelov Y. "Zero order drug delivery from double- layered porous ilms: release rate profiles from ethylcellulose, hydroxypropylcellulose and polyethyleneglycol mixtures". J Pharm Pharmacol, 1980, 32(4), 70. 28.
17. Korsmeyer, R., Gurny R., Doelker E., Buri P. and Peppas N., "Mechanism of solute release from porous hydrophilic polymers", Int J Pharm, 1983, 15(1), 25-35.

