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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF METOPROLOL SUCCINATE

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ABSTRACT

The main objective of the present study is to formulate Transdermal patch of Metoprolol Succinate for quick onset of action and avoid first pass effect thereby improving bioavailability. The designed to develop suitable Transdermal patch of Metoprolol Succinate, a beta-1 selective drug, it was quantified by UV spectroscopy at λmax of 223nm, using natural polymer with different ratios of Chitosan (a natural polycationic linear polysaccharide derived from chitin) with Di-butyl phthalate as a plasticizer and Dimethyl sulfoxide (DMSO) as a permeation enhancer, methanol as solvent system. Transdermal Patches containing Metoprolol Succinate were prepared by solvent casting technique-employing mercury as a substrate. Formulations F1, F2, F3, F4, F5, F6, F7 and F8 were composed of drug and Polymer with ratio 1:5. Evaluation parameter carried out for the Transdermal patch such as Thickness, weight variation, Moisture content, Drug content, folding endurance, In-vitro permeation study. Drug polymer interaction studies was carried out using FTIR studied showed there were no incompatibilities between drug and other excipients.

KEYWORDS: Metoprolol Succinate, Chitosan, Transdermal patch, Permeation enhancer, In-vitro drug release.

INTRODUCTION

Transdermal drug delivery systems are polymeric patches containing dissolved or dispersed drugs that deliver therapeutic agents at a constant rate to the human body. Currently,

transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin.

The transdermal route offers several advantages over conventional dosage forms such as tablets and injections, including avoidance of first-pass metabolism by the liver, minimization of pain, reduction of side effects, extended duration of activity, reduction in the fluctuations of drug concentrations in the blood, and possible sustained drug release. the highly organized structure of stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered.

The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery. Metoprolol Succinate is a drug used in the treatment of mild to moderate essential hypertension, Angina pectoris, Cardiac arrhythmias and myocardial infarctions. It acts by blocking ß1 the adrenoreceptors and is almost completely absorbed (95%) after oral administration, although the systemic bioavailability varies widely owing to extensive metabolism (40–60%).

Dose of Metoprolol Succinate (100-200 mg) daily. Peak plasma concentrations are achieved after 2–3 hours. The plasma half-life is about four hours, which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long—term treatment. Therefore, MS is an ideal drug candidate for transdermal drug delivery.

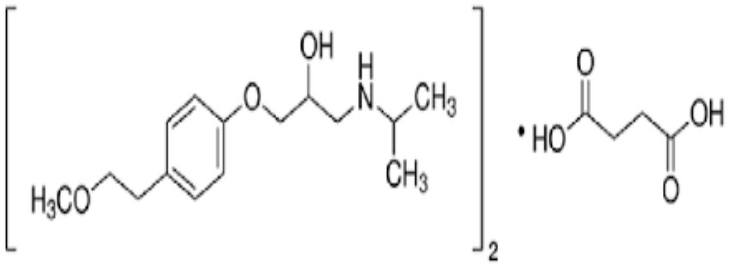

Fig 1: Metoprolol succinate.

MATERIALS AND METHODS

Metoprolol Succinate was obtained as a Gift sample from KP labs, Hyderabad, Chitosan, di-butyl phthalate, dimethyl sulfoxide were procured from Sree Srinivasa Scientifics, Hyderabad, methanol were procured from Chaithanya Scientifics, Vijayawada.

Preformulation studies

Methods of Determination of λmax

The Metoprolol succinate exhibits peak maximum absorbance at 223nm in 0.1N Hydrochloric acid.

Preparation of standard solution: 100mg of Metoprolol Succinate was exactly weighed in volumetric flask of 100 ml & solubilised in small volume of pH 7.4 phosphate buffer. The volume was made up with the 0.1N Hydrochloric acid to get a concentration of 1000µg/ml (SS-1). From this SS-2 was prepared containing 100µg/ml.

Formulation of Transdermal Patches

Transdermal Patches containing Metoprolol Succinate were prepared by solvent casting technique-employing mercury as a substrate. All ingredients are mixed with suitable solvents until all the ingredients dissolved. Metoprolol Succinate was added and stirred well in magnetic stirrer (20 min), until a homogeneous solution was obtained. The prepared solution was casted into a petridish and dried at room temperature for 24 hrs. The rate of evaporation was controlled by inverting the cut funnel over the Petridish. Membranes were taken out, cut into 3.14 cm^2, packed in aluminum foil and stored in desiccators until further use. The compositions of the transdermal patches were shown in Table no-1

Table 1: Composition of formulation.

Ingredients (in mg/ml)	F1	F2	F3	F4	F5	F6	F7	F8
Metoprolol Succinate	177	177	177	177	177	177	177	177
Chitosan	350	400	450	500	550	600	650	700
Di-butyl phthalate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Dimethyl sulfoxide	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Methanol	15	15	15	15	15	15	15	15

EVALUATION OF TRANSDERMAL PATCHES

FTIR study: The Infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded. The spectra obtained for Metoprolol Succinate, polymers, and physical mixtures of Metoprolol Succinate with polymers were compared. Disappearance of Metoprolol Succinate peaks or shifting of peak in any of the spectra was studied.

Thickness: The thickness of patches was measured by digital Verniercalipers with least count 0.01mm. The thickness uniformity was measured at five different sites and averages of five readings were taken with standard deviation.

Folding Endurance: It was determined by repeatedly folding a small strip of patches at the same place till it broke. The number of times, the patches could be folded at the same place without breaking gave the value of folding endurance.

Weight variation: Weight variation was determined by individually weighing randomly selected patches with the help of electronic balance. The average weight of a film and its standard deviation was calculated.

Percentage of moisture loss: The percent moisture loss was carried out to check the integrity of the patch at dry condition. This was carried out in the following manner. The patches were weighed accurately and kept in the desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed.

Percentage of moisture loss formula

Percentage of moisture loss= initial weight-final weight/initial weight x 100

Percent moisture absorption

The patches were accurately weighed and placed in desiccators contains humidity condition of 80-90% is maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained then taken out and weighed. The percentage moisture uptake was calculated as the difference between final weight (W_2) and initial weight (W_1) with respect to initial weight.

Percent moisture absorption formula:

Percent moisture absorption= $(W_2-W_1) / W_1 X 100$

In vitro drug release studies

The in-vitro permeation studies of all the formulations were carried out using Franz diffusion cell as described in the methodology section using egg membrane as a permeation membrane for the study. The comparative cumulative percentage drug permeation data of all the formulations F1 to F8. The optimized formulation F7 containing maximum concentration of chitosan showed highest % drug permeation at the end of 8 hrs and hence this formulation was selected as optimized formulation for further study. It was revealed that chitosan concentrations were having positive effect on the drug permeation through the membrane.

RESULTS AND DISCUSSION

Our present work comprises the formulation and evaluation of Metoprolol Succinate transdermal patches for sustained or extended release for a prolonged period of time. Transdermal patches of metoprolol succinate were prepared by solvent evaporation method. Totally, 8 formulation trials (F1 to F8) were done with the aim to achieve the successful matrix type Metoprolol Succinate transdermal patches. Chitosan polymer in the formulation of Metoprolol Succinate transdermal patches individually. Methanol used as solvents. Dibutyl phthalate used as plasticizer and dimethyl sulfoxide used as a penetration enhancer. The compatibility study of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FTIR studies. All the patches were evaluated for weight variation, thickness, percentage moisture absorption, percentage moisture loss, folding endurance, and in-vitro drug release. In this thickness study with the help of Digital verneircalipers, the thickness of patches was measured. It was found to be in between 0.15±0.015 to 0.18±0.019. All formulations have good film properties. The folding endurance of the patches was found between 184±3.22 to 204±1.88, the results indicate, as the Chitosan concentration increases the folding endurance of the patches increases. All formulations from F1 to F8 show weight variation in between 487±0.001 to 536±0.003 gm. The percentage moisture absorption of the prepared patches results between 3.03±0.21 to 7.49±0.88. The percentage moisture Loss of the prepared patches results between 1.29±0.03 to 4.98±0.06. From the results of In - vitro drug diffusion studies results between 80.14±0.052 to 93.21±0.08. Formulation F7 containing chitosan as ideal formulation for Metoprolol succinate because it showed better release with sustained effect as compared to other formulations. The Cumulative drug release from Formulation F7 was found to be (85.203±0.32), after 24 hrs. The drug release kinetics studies showed higuchi with peppas mechanism of drug release.

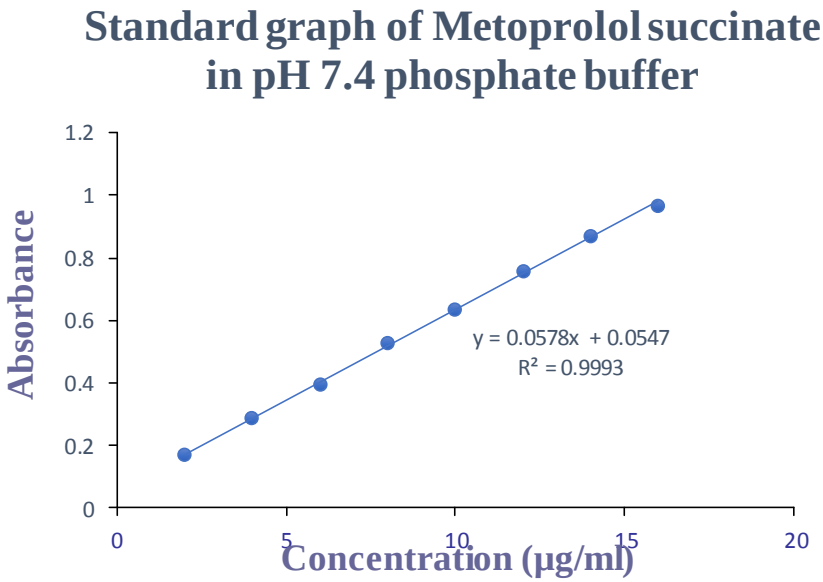

Fig no 2: Standard graph of metoprolol succinate.

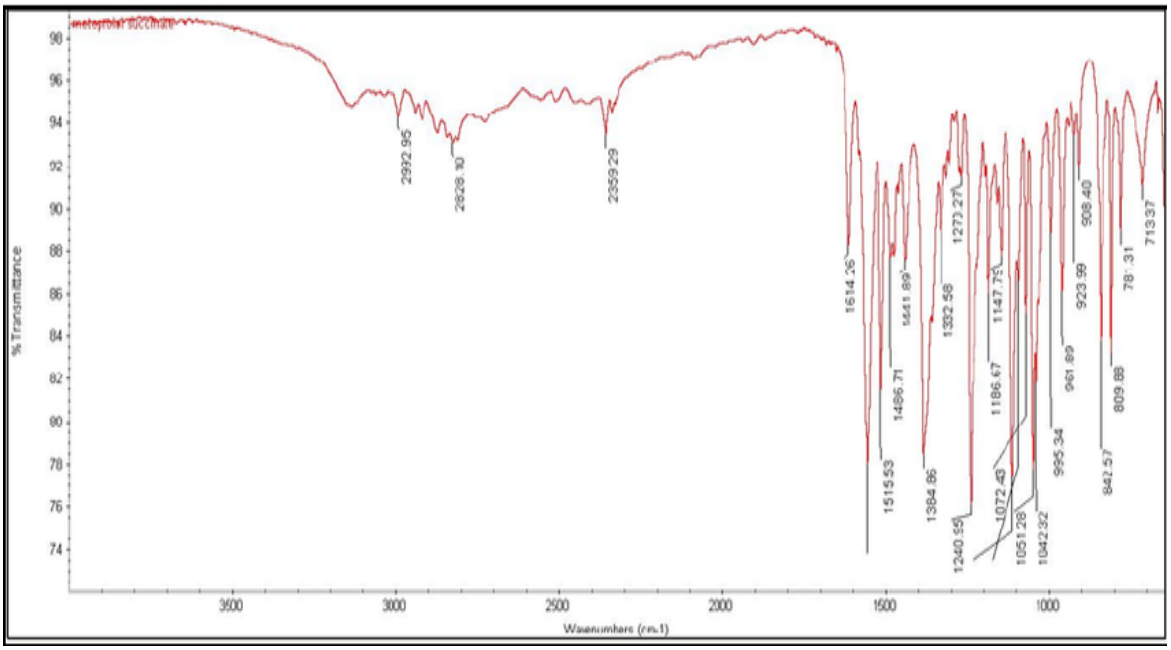

Figure no: 3 standard geaph of metoprolol succinate.

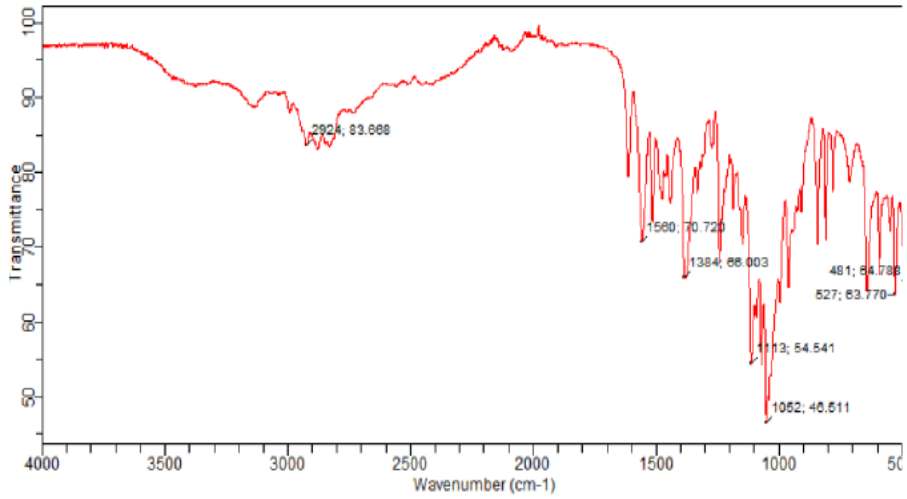

Figure no: 4 FTIR spectra of optimised formulation.

Formulation of Transdermal Patches

Transdermal Patches containing Metoprolol Succinate were prepared by solvent casting technique-employing mercury as a substrate. All ingredients are mixed with suitable solvents until all the ingredients dissolved. Metoprolol Succinate was added and stirred well in magnetic stirrer (20 min), until a homogeneous solution was obtained. The prepared solution was casted into a petridish and dried at room temperature for 24 hrs. The rate of evaporation was controlled by inverting the cut funnel over the Petridish. membranes were taken out, cut into 3.14 cm^2, packed in aluminum foil and stored in desiccators until further use. The compositions of the transdermal patches were shown in Table no-1

Table no: 2 Result of Evaluation parameters.

formulation	Weight uniformity (gm)±SD	Folding endurance ±SD	Thickness (mm)±SD	% moisture loss ±SD	% moisture absorption ±SD	% drug release ±SD
F1	536±0.003	194±2.23	0.17±0.020	4.98±0.06	6.35±0.034	87.65±0.031
F2	524±0.001	188±2.36	0.18±0.025	2.94±0.005	4.13±2.23	80.14±0.052
F3	530±0.002	197±2.87	0.15±0.015	3.36±0.02	6.22±199	85.20±0.031
F4	533±0.002	190±3.11	0.16±0.019	4.23±0.03	7.49±0.88	89.32±0.032
F5	511±0.003	201±1.24	0.17±0.013	2.13±0.04	4.07±0.21	81.01±0.004
F6	496±0.004	195±1.45	0.18±0.019	3.82±0.01	3.08±0.13	91.54±0.024
F7	494±0.002	204±1.88	0.15±0.031	1.29±0.03	3.03±0.21	93.21±0.08
F8	487±0.001	184±3.22	0.16±0.013	2.56±0.04	4.2±0.06	89.20±0.028

Table no: 3 In vitro cumulative percent drug release of Metoprolol Succinate Trnasdermal Patch.

Time (hrs)	Cumulative percentage drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	2.75±0.12	11.63±0.26	13.5±0.26	17.8±0.28	15.36±0.26	18.66±0.28	17.47±0.21	11.58±0.23
1	8.96±0.24	13.85±0.28	24.06±0.34	21.9±0.37	20.12±0.37	23.83±0.34	21.93±0.33	20.36±0.34
2	19..87±0.34	29.35±0.39	35.21±0.51	28.1±0.42	29.35±0.40	39.54±0.48	39.54±0.50	27.12±0.44
3	26.12±0.40	33.25±0.44	37.9±0.53	39.13±0.51	37.91±0.53	43.28±0.44	46.98±0.52	36.85±0.47
4	30.25±0.39	39.61±0.48	43.25±0.49	57.32±0.60	46.82±0.53	50.01±0.51	53.96±0.51	42.39±0.49
5	35.27±0.54	42.73±0.46	54.210.58	66.21±0.66	50.82±0.57	59.88±0.58	64.21±0.54	49.58±0.50
6	47.39±0.57	51.97±0.51	62.58±0.53	70.8±0.69	55.94±0.59	63.98±0.55	73.54±0.63	51.36±0.52
7	50.01±0.51	58.21±0.55	69.58±0.57	75.36±0.72	6.12±0.55	70.64±0.70	82.05±0.77	57.25±0.55
8	56.04±0.52	65.87±0.59	74.04±0.71	79.23.6±0.74	66.12±0.61	76.06±0.74	88.20±0.79	62.92±0.58

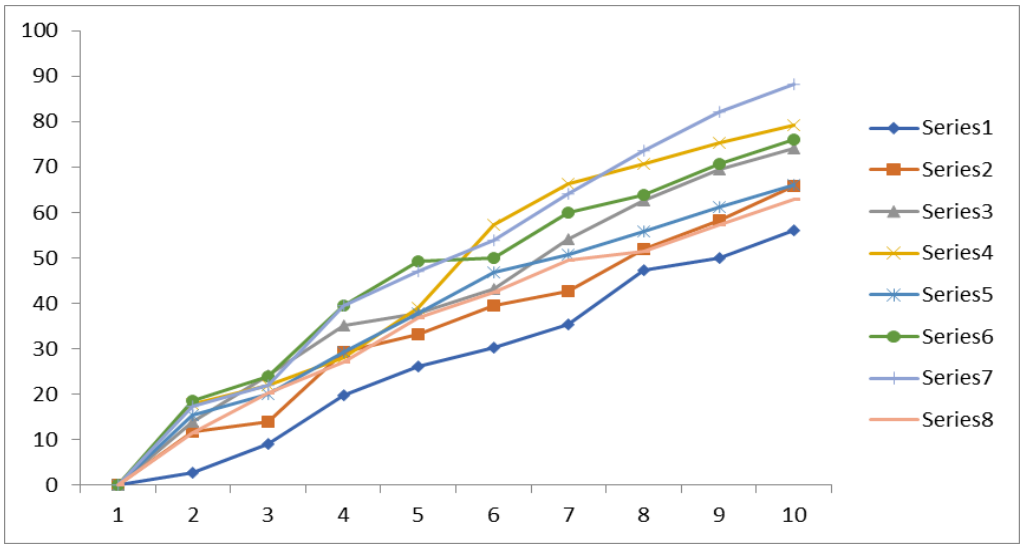

Figure no: 5 In-vitro cumulative percent drug release profiles of Metoprolol Succinate Trnasdermal Patch.

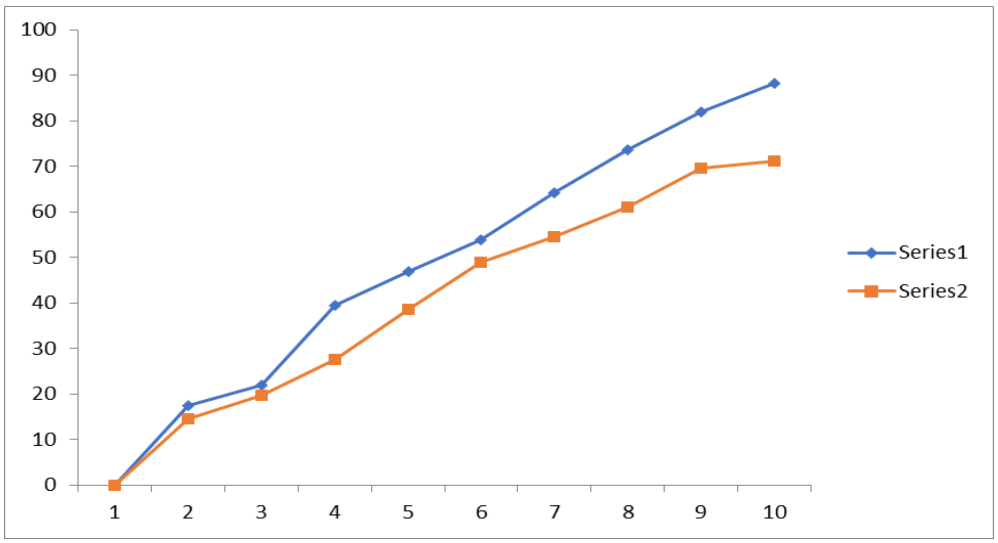

Figure no 6: Comparison of optimized formulation with the marketed formulation.

Kinetics of in-vitro drug release (curve fitting analysis)

To study the drug release kinetics of transdermal patch of metoprolol succinate, different kinetic equations were applied to interpret the release from matrices. The linear nature of curves obtained for zero order and first order, higuchi and peppas model demonstrated by very close and higher R^2values suggests that the release from the formulations, may follow any one of these models. The kinetic in vitro diffusion profile of best formulation (F7) were fitted into zero, first, higuchi and peppas equations. They showed highest linearity with higuchi order release.

Table no: 4 Kinetics of In-vitro permeation studies of optimized formulation.

	Zero order	First order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F7	0.990	0.369	0.991	0.928

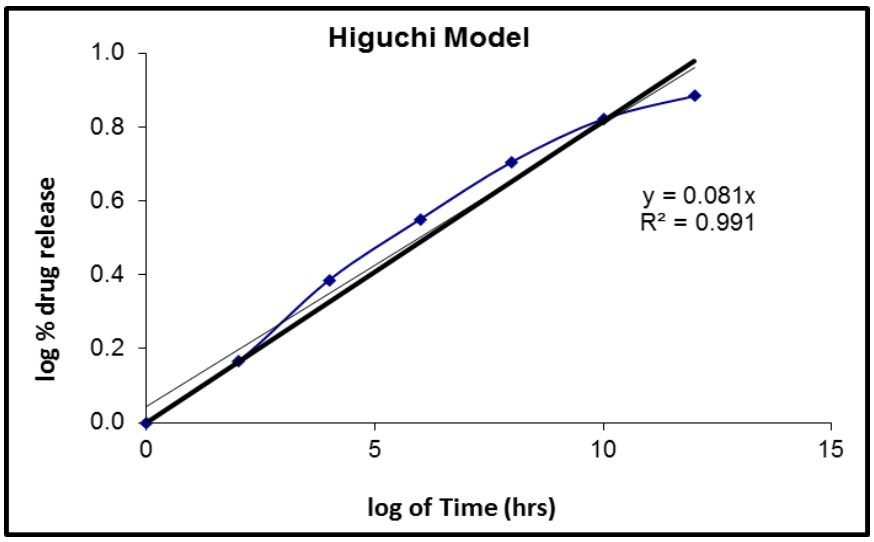

Fig no 7: Higuchi release graph.

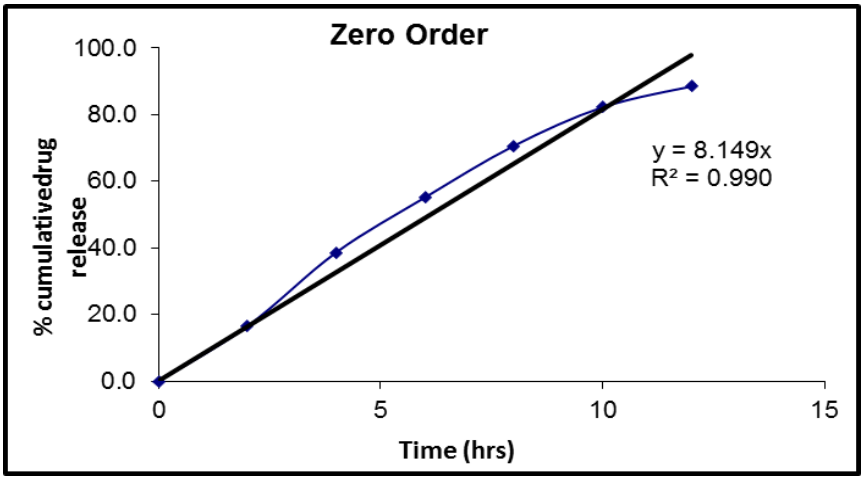

Fig no 8: Zero order kinetics graph.

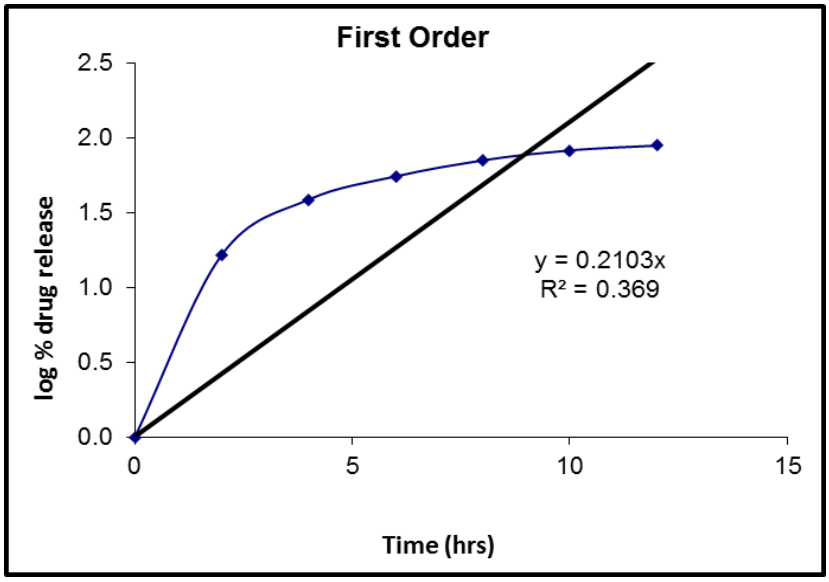

Fig no 9: First order kinetics graph.

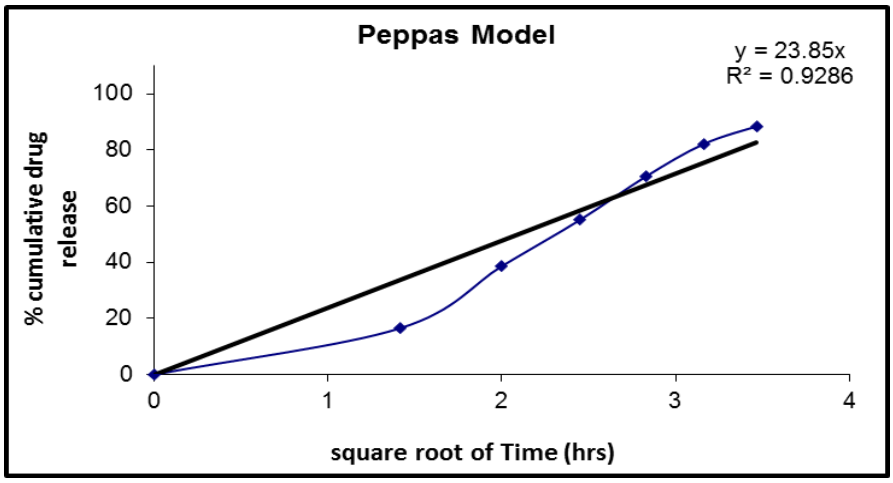

Fig no 10: Peppas release graph.

CONCLUSION

It is observed that the drug is having good correlation between drug release and drug permeation by In vitro studies. It can be concluded that such a patches of Chitosan could be a good carrier in transdermal delivery of Metoprolol Succinate. FTIR studies of Chitosan, Metoprolol Succinate and final formulation was seen and peaks found to be within the range with no significant deviation. Hence can be concluded that there are no interactions between drug and polymers. Metoprolol Succinate is an anti-hypertensive agent which selected for the preparation of transdermal delivery system as it complies with physicochemical properties required to permeate through skin. The pre formulation studies involving solubility, melting point, partition coefficient and pH of the drug were found to be comparable with the standard. It may also concluded that adhesion of transdermal drug delivery patch to skin membrane

leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug. All the formulated transdermal patches were visually inspected for physical parameters such as Weight variation, Thickness, Folding endurance, Moisture absorption, Moisture loss and all the results were found to be within the Pharmacopoeial limits. The prepared Metoprolol Succinate Transdermal patches were evaluated for In-vitro permeation studies using egg membrane. Among all the 8 formulations F7 formulation was shown 85.20% cumulative drug release within 8 hrs. The kinetics of In-vitro permeation studies for F7 formulation was plotted and followed the Higuchi mechanism of drug release.

ACKNOWLEGMENT

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