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Formulation and Evaluation of Transdermal Patch of Glibenclamide

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Abstract

The plan of the present research study was to prepare Glibenclamide transdermal patches and to study the effect of two polymer combination and polymer ratios on physiochemical parameters including in-vitro drug release profile. Glibenclamide transdermal patches were prepared using Chitosan is the main natural polymer and Hydroxy propyl methyl cellulose (HPMC) in different ratios. Dibutylphthalate was used as a plasticizer and oleic acid used as permeation enhancers which were prepared by solvent casting method. The prepared formulations were evaluated for various in vitro parameters like Thickness, Weight variation, Folding endurance, Moisture absorption, Moisture loss, Drug content, Drug permeation, In-vitro drug release studies were performed by using Franz diffusion cells. The FT-IR studies revealed no interaction between drug and polymers. Chitosan and HPMC is better formulation for control release of drug up to 8 hrs of time.

However the in vitro drug release of the best formulation F4 follows zero order kinetic and the mechanism of the present study encourage that the Glibenclamide transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized.

Keywords: Transermal Patch, Glibenclamide, HPMC

Introduction

Today about 70% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy and differs from traditional topical drug delivery. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form.

Glibenclamide is a poor water solubility, Dose 5-15 mg per day shorter half-life, lipophillic M.P.169- 170° appropriate, molecular weight 494.08 ,Duration of action 12-24 hour and Half life1.4-1.8 hours 10 hours.

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Glyburide, a second-generation sulfonylurea antidiabetic agent, lowers blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. High dose may be cause severe hypoglycaemia, Diarrhea, Constipation, Indigestion, Increased appetite. Hence this drug is suitable for tdds. Chitosan is a polysaccharide extracted from the shells of crustaceans, such as shrimp, crab and other Chitosan is widely used as an excipient in oral and other pharmaceutical formulation, and also used in cosmetics. It is regarded as nontoxic and non-irritant material and it also act as Permeation enhancer, Used in controlled drug release dosage form it posses good Film forming ability, Bioadhesive, Biodegradability and Bio compatibility.

Material and Methods

Glibenclamide was obtained as gift sample from emcure Pharmaceuticals Ltd Gujarat, India. HPMC procured from AR chemicals. Other excipients used were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Preformulation Studies

The preformulation studies provide the type of information needed to define the nature of the drug substance this information provides the frame work for the drug's combination with pharmaceutical ingredients.

Solubility

A qualitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa.after each addition, the system is vigorously shaken and observed visually.

Melting Point

It is used to determine the purity of the drug. The melting point should be in the range as described

Loss on Drying

Weighed amount of drug was taken in Petri dish and is kept for drying in oven for 1 hour at 100^0C initial weights was taken and after hour final weight was taken and loss on drying was calculated.

Partition Coefficient

25 ug/ml solution of pure drug in octanol was prepared. The mixture of the 1:1 ratio of octanol and phosphate buffer pH 7.4 was properly mixed for half hours in separating funnel. The mixture was added to drug solution and allowed to stand for one hour. Then centrifuged the mixture 5000 rpm in 25^0C the mixture was separated and absorbance was measured by UV spectroscopy.

IR spectrophotometric studies

Infra red spectrum of any compound gives information about the group present in particular compound. Small quantity of drug was mixed with oil and one drop placed between KBr pellets and spared uniformly.The pellets were placed in holder and infrared spectra was taken various peaks in infrared spectrum were interpreted for presence of different group in the structure of drug.

UV Spectrophotomatric studies

The UV spectroscopic study is performing their role as an addition for drug identification tools. UV spectrums of drug in different solvents were obtainedby making the solution of drug in different solvents and analyzing this solution using UV-visible spectrophotometer. The spectrum obtained was compared with the standard. (Shimadzu UV-visible spectrophotometer, model UV-1700). Accurately weighed 10mg of drug was dissolved in 10 ml of projected solution in 10ml of volumetric flask and prepared suitable dilution. The spectrum of this solution was analyzed in 275-300 nm range in UV/Visible spectrophotometer and compared with the standard.

Preparation of standard stock solution

Weighed accurately 10 mg of candidate drug and transferred to 100 ml of volumetric flask. Phosphate buffer pH6.8 was added to dissolve the drug completely. Maked up the volume up to 100 ml by phosphate buffer pH 6.8.

Preparation of standard calibration curve of candidate drug in phosphate buffer pH 6.8

From above solution various dilutions were prepared to get concentration, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml. The graph of concentration v/s absorbance was plotted and data was subjected to linear regression analysis λ_{max} being 300 nm.

Calibration curve of drug in standard phosphate buffer pH 7.4

Phosphate buffer 7.4 media was prepared by taking 2.38 g sodium hydrogen phosphate, 0.19 g potassium di hydrogen phosphate, 8.0 Nacl make

up to 1000 ml with distilled water. Calibration curve of in PBS pH 7.4 is shown in below.

Preparation of Standard Calibration curve of candidate drug in distill water

From above solution various dilutions were prepared to get concentration, 2, 4, 6, 8, 10, 12, 14, 16, 18,20 µg/ml The graph of concentration v/s absorbance was plotted and data was subjected to linear regression analysis λ_{max} being 275 nm .

Compatibility Studies

Drug excipients interaction

Compatibility of the drug with excipients was determined by differential scanning calorimetry (DSC) analysis. This. The samples were taken for DSC study included Glibenclmide, Physical mixture and individual polymers.

Physical observation

The drug and excipients were kept at different temperature 2-8°C, at room temperature and 60°C and all samples were physically observed after 1 week for a period of 4 weeks.

Formulation and optimization of transdermal film

Formulation of Blank Films

Solvent Casting Technique was employed in the preparation of blank films. Solution of Chitosan/HPMC blend and were prepared by dissolving the specified amount of polymer in 1.0% w/v Acetic acid solution and the solution of HPMC was prepared by dissolving in a mixture of water and ethanol (8:2) respectively. To the above prepared Solution 30% w/w (with respect to dry weight of polymer) of DBT was added and stirred for 30 min. The above solution (10ml) was poured into a Petri dish and kept in an oven at 40◦c for complete drying. The dried films were removed from the Petri dish and stored in desiccators until use.

Formulation of Drug Loaded Films

Solvent Casting Technique was employed in the present work for the preparation of drug films.Solution of plain Chitosan and Chitosan/ HPMC blend were prepared by dissolving the polymer in1.0% w/v Acetic acid solution, and the solution of HPMC was prepared by dissolving in a mixture of water and ethanol (8:2) respectively. To the above polymeric solution 30% w/w (with respect to dry weight of polymer) of DBT and was added. DBT was used as a plasticizer in the preparation of films. 10 mg of Glibenclamide was added and stirred for 30 min. and penetration enhancer was added. Drug containing polymeric solution (10ml) were poured into a Petri dish, and kept in an oven at 40◦C for complete drying. The dried films were removed from the Petri dish and stored in desiccators until use.

Table 1: Composition Of Drug

S. No.	Ingredient	Formulation								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug (mg)	10	10	10	10	10	10	10	10	10
2	Chitosan % (w/v)	25	25	25	50	50	50	75	75	75
3	HPMC % (w/v)	25	50	75	25	50	75	25	50	75
4	DBT % w\v	30	30	30	30	30	30	30	30	30
5	Oleic acid	5	5	5	5	5	5	5	5	5
6	Ethanol : Water	8:2	8:2	8:2	8:2	8:2	8:2	8:2	8:2	8:2

F1 to F9 batch based on two parameter drug content and in vitro drug release

Drug content determination

The patch area was cut and dissolved in distill water the solvent ethanol and di chloro methane, to make polymer soluble, were added to the mixture and the remaining volume was made up with distill water to 100 ml volumetric flask. Then 1ml was withdrawn from the solution and diluted to 10 ml. the absorbance of the solution was taken at 275 nm and concentration was calculated.

Study the effect of varying concentration of polymer on in vitro drug release

The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. In vitro studies are also done for TD development. The fabricated film was placed on the semi permeable membrane and attach to the modified diffusion cell such that the

cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH at 7.4 at 37±10˚C. The elution medium was stirred magnetically. The aliquot (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of 7.4. the sample were analyzed for drug content using UV spectrometer at 275 nm. The observation are shown in table no.6.3,6.4,7.5 and three corresponding graph are shown in fig

Evaluation of optimized batch

Based on the drug content and drug release of the various batch optimized batch was found to be the optimized batch of Glibenclamide were evaluated or the various parameter such as

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. The Individual weight should not deviate significantly from the average weight.

Thickness

The thickness of film was determined by measuring the thickness at centre and side on the formulated polymeric film using (micrometer) screw gauge and the average thickness was determined. The least count of screw gauge and average thickness was determined. The least count of screw gauge was found to be 0.01cm.

Folding endurance

Folding endurance of the film was determined by repeatedly folding a small strip of film (2cm×2cm) at the same place till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance.

Moisture content

The film were weighed individually and kept at desiccators containing activated silica at room temperature for 24hours. Individual film was weighed repeatedly until they show the constant weight. The percentage of moisture content was calculated as the difference between the initial and final weight with respect to final weight.

Percent Moisture Loss

The film were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs .individual films were weighed repeatedly until they showed a content weight. The percentage o moisture content was calculated a difference between initial and final weight with respect to final weight.

Percent moisture absorption

A weighed film kept in desiccators at room temperature at room temperature for 24 hrs was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in dessicater until a constant eight for the film was obtained.

Swelling Index

Weighed pieces 1×1 cm^2 of film were immersed in distilled water at 5,10,30 and 60 min. Soaked films were removed from the medium at predetermined time. Blotted to remove excess liquid and weighed immediately. The swelling index was calculated from the weight increase, as follows.

Swelling Index = W2-W2\W1

Where W1 and W 2 are the weight of the film before and after immersion in the medium respectively.

Flatness

Longitudinal strips were cut out from each film. One from the each film one from the center and two from either side. The length of each strip was measured and the variation in the length because of non uniformity flatness was measure and the variation in length because of non uniformity in Flatness was measured by determining percent constriction considering 0% constriction is eq. to 100% constriction 1 eq to100% flatness.

Percentage of Constriction= L_1-L_2×100

***In vitro* permeation study**

The *in vitro* permeation study of fabricated transdermal patch of Glibenclamide was carried out by using cellophane membrane and Franz diffusion cell. The membrane was sandwiched between donor and receptor compartment of the diffusion cell. A diameter patch was placed in initiate contact with the membrane the back side was covered with aluminum foil act as a backing membrane was place in the receptor compartment filled with 17 ml of phosphate buffer pH 7.4. The cell content was stirred with a magnetic stirred with a magnetic stirrer and a temperature of 37+-5˚C was maintained during experiment. Withdraw 1 ml of sample through the sampling post different time interval for a period 24 hr,

simultaneously replacing equal volume of phosphate buffer pH 7.4 to maintained an ink condition. The sample was analyzed spectrophotometer at 275nm.

Stability study

The formulations were stored at 40 ± 2°C&75 ± 5% RH for one month by storing the samples in a stability chamber.Sample of batch F4 was packed in amber colored bottles, which were tightly plugged with cotton and capped with aluminium.they were then stored at 25ºC and 60%RH ,30%C,65%RH,and 40ºC &75% for 3 month and evaluated for their drug cumulative release and physical appreance study.The formulation F4 calculated initially .the formulation 7 was kept in stability chamber. After 15 days and then 30 days, the %drug content was calculated.

Analysis of Release Mechanism of Optimized Formulation

In order to examine the release mechanism of drug sample from the prepared transdermal patch o the optimized formulation , the result of the percent cumulative drug release was examined in accordance to the kinetic model such as zero order, first order, higuchi equation, kromeyer-peppas equation and Hixson Crowell equation. The model that best fits the release data is selected based on the correlation coefficient Value I various models. The model that gives high r value I considered as the best fit of the release data. A graph is plotted between the log time on x axis and the log cumulative percentage of drug release on y axis an it gives a straight line.

Results and Discussion

The preformulation testing is the first step in development of dosage forms of drug substance. These investigations may confirm that there are no significant barriers to dosage form development. Organoleptic properties study, solubility study, loss on drying, Identification and authentification of drug, Partition coefficient, quantitative estimation of drug and compatibility study were carried out during preformulation study. These tests were performed as per procedure given in preformulation part. The results were found in table. The preformulation studies involving description, solubility, melting point, of the drug were foun. Based on the all the above preformulation studies the drug was suitable for making the Transdermal formulation. The patches were transparent, smooth and flexible. The optimized batch was selected on the base of drug content and in vitro drug release study by diffusion study. The optimized batch was found to be batch F4.The optimized batch was evaluated for various evaluation parameters.

The result of weight variation, thickness, moisture content, moisture uptake, folding endurance, drug content are shown The patch exhibits uniform weight and thickness F4-0.192 ± 0.016 mm. as the thickness was Indicates less patch was most suited for high release of medicament a controlled rate The folding endurance F4 was found to be 200.7±1.50 which was optimum and during stretching and handling it was less fragile. The moisture content of F4 was found to be 0.68±0.075 so less chances of microbial contamination during prolonged storage. The drug content F4 was found to be 96.25±0.6% .The swelling index was found to be 5 ,10, 30, 60 min result was indicated that 67.7, 68.5, 72.5, and 75.8.The % flatness was measured 98% this shows the flat surface. Stability study showed that the preparation was most suitable during storage at 40±75% RH and percentages cumulative result did not vary with time. There were no color change and no leakage during storage at highly humid condition.

Stability study showed that the preparation was most suitable during storage at 40±75% RH and percentages cumulative result did not vary with time. There were no color change and no leakage during storage at highly humid condition. Based on all this factor the trans dermal drug delivery system F4 is having greater % drug release. The formulation F4 shows better extended release up to 8 hrs when compared to other formulation. So it was concluded that the formulation F4 prepared by using Chitosan and HPMC is better formulation for control release of drug up to 8 hrs of time.

The percent cumulative drug release of F4 was found to be 67.110 ± 2.073. the uniform thickness indicates that the polymeric solution of the drug is well dispersed is the patch In vitro permeation studies of patch using cellophane membrane barrier was carried out using modified diffusion cell. The result of in permeation studies optimized formulation F4 is 8 hours result is 56.70 ±

0.64.The releases kinetic was evaluated by making use of zero order, first order, Higuchi diffusion and Krosemeyer Peppas equation and Hixon Crowell equation. In zero order model, graph was plotted between percent cumulative drug release versus time was found be linear the value of regression coefficient was R2 = 0.997. The optimize formulation follows the zero order model model. However the in vitro drug release of the best formulation F4 follows zero order kinetic and the mechanism of the present study encourage that the Glibenclamide transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized.

Table 2: Organoleptic and Physical Properties of Drug Sample

S.No.	Test	Observations	Standards
1	Color	White	White
2	Taste	Tasteless	Tasteless
3	Odor	Odorless	Odorless

Table 3: Organoleptic and Physical Properties of Drug Sample

S.No.	Material	Observation	Standard	Inference
1	Glibenclamide	0.12	0.1	The log P value was found to be close to standard ,it shows that drug is sufficiently lipophilic and pure

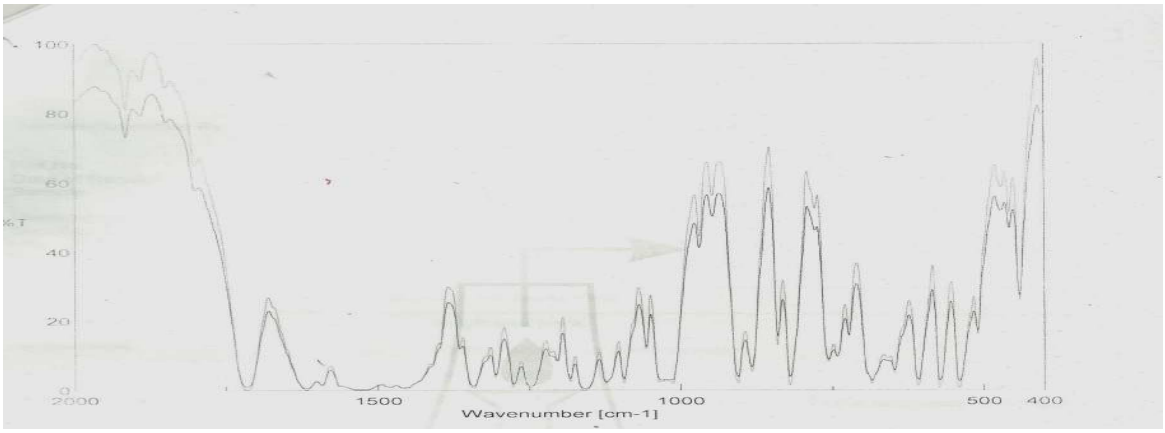

Fig. 1: IR spectra of Glibenclamide

Table 4: Calibration curve of drug in phosphate buffer pH 6.8

S/No.	Concentration (µg/ml)	Absorbance
1	2	0.043
2	4	0.091
3	6	0.130
4	8	0.180
5	10	0.220
6	12	0.259

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7	14	0.308
8	16	0.352
9	18	0.403
10	20	0.450

Table 5: Calibration curve of drug in 7.4

S/No.	Concentration (µg/ml)	Absorbance
1	0	0.00
2	2	0.040
3	4	0.083
4	6	0.134
5	8	0.166
6	10	0.240
7	12	0.280
8	14	0.310
9	16	0.310
10	18	0.360
11	20	0.391

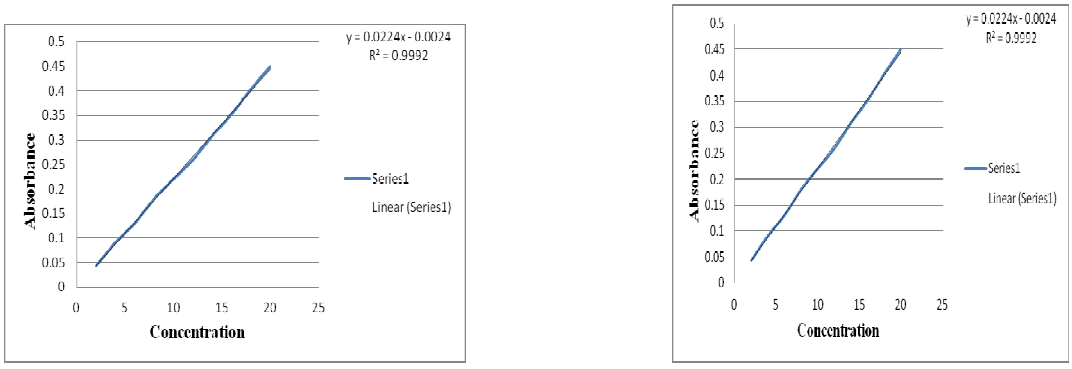

Fig. 2: Calibration curve of drug in phosphate buffer pH 6.8 and 7.4

Table 6: UV spectroscopic studies of Glibenclamide sample

S/No.	Solvent	Peak point observed	Peak point specified (IP 2007)
1	Phosphate buffer pH 7.4	275	275-300

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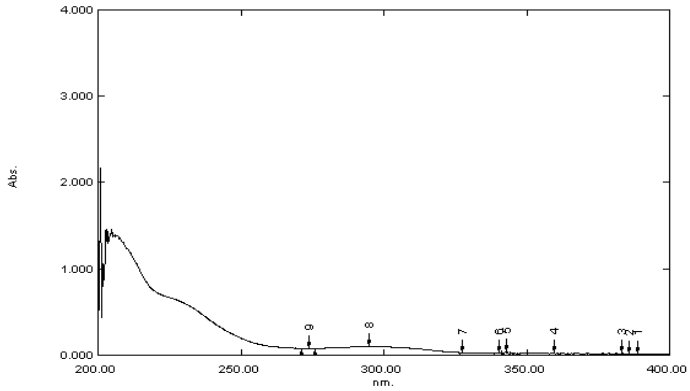

Fig. 3: UV Spectra of drug

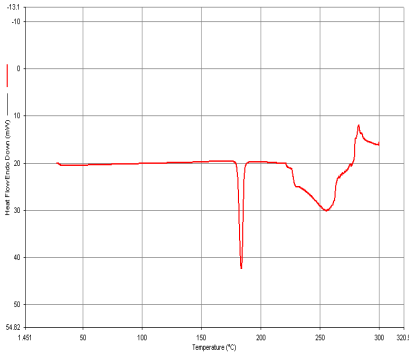

Fig. 4: DSC Thermogram of drug

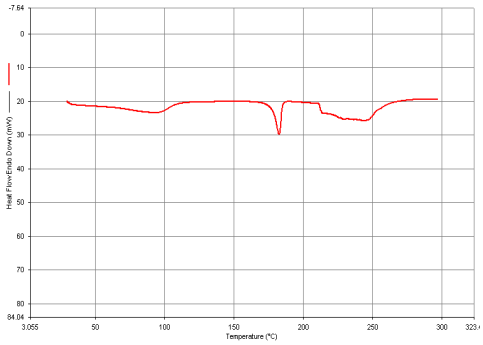

Fig. 5: DSC Thermogram of Physical Mixture

Table 7: Physical compatibility of drug and excipient

S. No.	Sample	Color	Observation at refrigerator (5 ± 3°C)	Observation at room temperature (25 ± 2°C)	Observation at temperature (60 ± 2 °C)
1	Glibenclamide	White	No change	No change	No change
2	Drug+ chitosan	White	No change	No change	No change
3	Drug+HPMC	White	No change	No change	No change
4	Drug + DBT	White	No change	No change	No change
5	Drug+Oliec acid	Light yellow	No change	No change	No change
6	Drug+ All Excipients	Light yellow	No change	No change	No change

Table 8: Drug Content Determination

S. No.	Formulation Code	Drug Content
1	F1	66.96 ± 0.41
2	F2	72.92 ± 1.1
3	F3	69.96 ±1.2
4	F4	96.25 ± 0.6
5	F5	86.71 ± 1.8
6	F6	65.61 ± 0.9

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7	F7	74.33 ± 1.4
8	F8	88.37 ± 0.7
9	F9	76.26 ± 0.92

Data shows mean ± of S.D of three Formulations

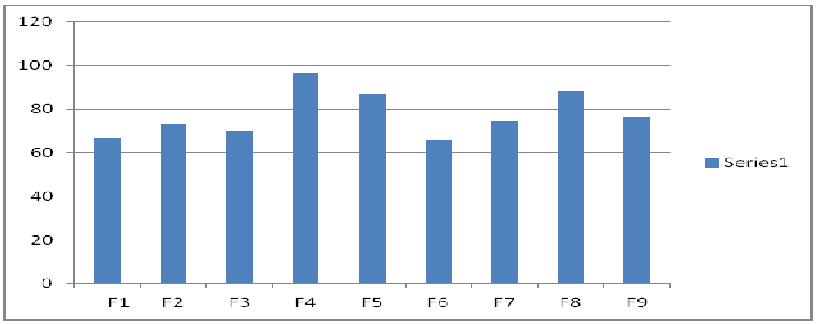

Fig. 6: Drug content of different formulation

Table 9: % CDR of formulation F5, F8, and F4

S/No.	Time (hrs)	Percent cumulative drug release Different Formulation		
		F5	F8	F4
1	0	0.000 ± 0.00	0.00 ± 0.00	0.000 ± 0.000
2	1	5.679 ±1.055	5.835 ±2.057	7.702 ± 1.009
3	2	11.496±2.007	10.670±1.004	11.987±2.060
4	3	19.575±1.007	18.103±1.0004	17.409±2.004
5	4	27.588±1.005	23.752 ± 2.005	25.673±2.005
6	5	34.572±3.006	30.808 ± 3.006	34.614±3.005
7	6	43.016±1.005	38.761 ± 2.005	43.740±3.005
8	7	50.904±2.005	46.308 ± 1.006	54.201±2.004
9	8	52.862±3.789	54.057±2.0055	63.794±2.038

Table 10: Evaluation parameter for F4 batch

S/No.	Evaluation parameter	Result
1	weight variation	0.45 ± 0.02
2	Thickness	0.192 ± 0.016
3	Folding Endurance	200.7±1.50
4	% Moisture content	0.68±0.07
5	%Drug Content	96.25 ± 0.6
7	% Moisture Absorption	291±3.18

Table 11: Swelling Index of F4 batch

S/No.	Batch	% Swelling Index			
		5 min	10 min	30 min	60 min
1	F4	67.1	68.5	72.5	78.5

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Table 12: Drug Permeation of Optimized Formulation

S/No.	Time (hrs)	Absorbance
1	0	0
2	1	7.03 ± 0.44
3	2	12.15± 0.95
4	3	19.27± 0.21
5	4	25.26 ± 0.60
6	5	34.37± 5.57
7	6	41.97 ± 0.81
8	7	48.44 ±0.72
9	8	56.70 ± 0.64

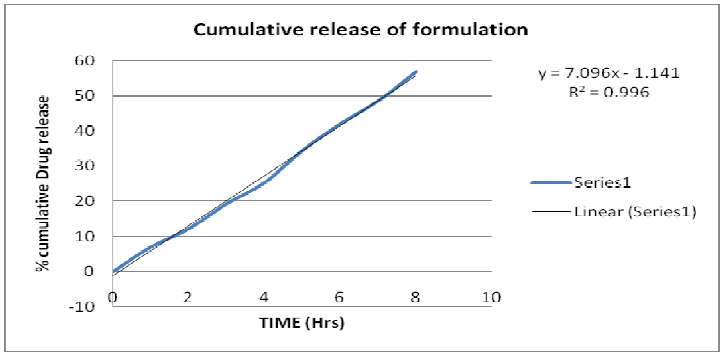

Fig. 10: Cumulative release of formulation

Table 13: Stability study data of drug content uniformity of optimized formulation

Optimized formulation	Percent cumulative drug release		
F4	Initially	After 15 days	After 30 days
	0.36 ± 0.40	0.34 ± 0.32	0.25±0.36

Table 14: Color and leakage observed in the formulation

Optimized formulation	Appearance		
F4	Initial appearance of film	After 15 days	30 days
	Off white	No change	No change

Table 15:Analysis of drug release kinetics

S/No.	Time T hrs	CDR (Q)	√t	Log t	% Q	Log % Q	% Drug Remained	Log% Qr	3√ Qr
1	0	0.000	0.000	0	0	0	100	4.605	4.641
2	1	8.245	1.000	1.414	7.03	0.698	91.753	4.459	4.510

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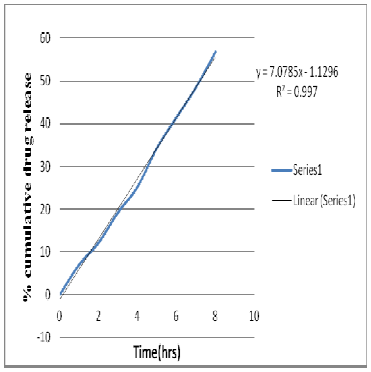
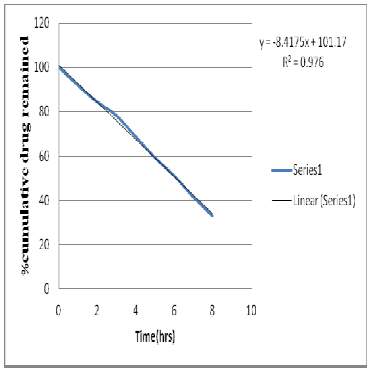
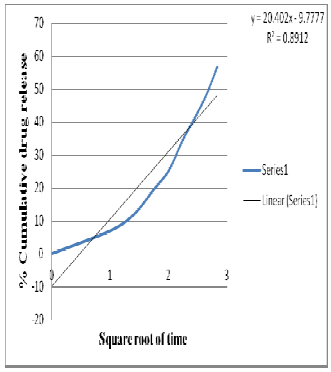
3	2	15.631	1.414	0.301	12.15	0.740	84.369	4.435	4.386
4	3	21.897	1.732	0.477	19.27	0.869	78.103	4.358	4.275
5	4	31.299	2.000	0.602	25.26	1.008	68.701	4.229	4.096
6	5	40.766	2.236	0.698	34.37	1.056	59.234	4.081	3.898
7	6	49.007	2.449	0.778	41.44	1.136	50.993	3.931	3.708
8	7	58.576	2.646	0.846	48.44	1.193	41.424	3.725	3.460
9	8	67.110	2.828	0.903	56.70	1.298	32.89	3.493	3.204



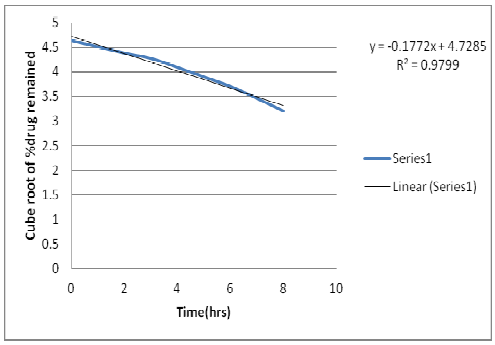
Zero Order Modal(F4)



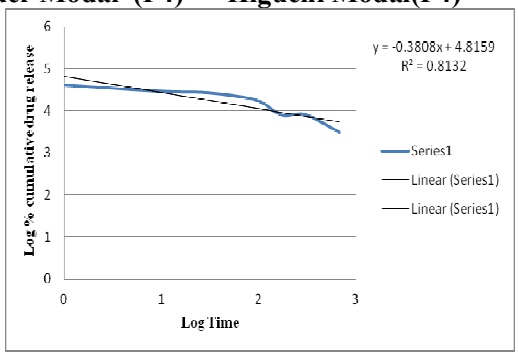
First Order Modal (F4)



Higuchi Modal(F4)



Hixon-Crowell Model (F4)



kross meyer and peppas (F4)

Table 16: Models and their R^2 values of optimized formulation

S/No.	Modal	R^2
1	Zero order	0.997
2	First order	0.976
3	Higuchi	0.891
4	Hixson -Croswell	0.979
5	Krosmeyer- peppas	0.813

Conclusion

Delivery via the transdermal route is an interesting option is this respect because transdermal route is convenient and safe. This offers several potential advantage over conventional route like avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drug, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter and intrapatient variation and most importantly, it provide patient compliance as the drug delivery is painless.

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