Research Article

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FORMULATION AND DEVELOPMENT OF NEW TRANSDERMAL DOSAGES OF DILTIAZEM

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Abstract: The objective of this research work is formulate And develop the New Transdermal dosages of Diltiazem. Research work includes preformulation studies which involving description, solubility, melting point, of the drug were found to be comparable with the standard. Based on the all the above preformulation studies the drug was suitable for making the transdermal formulation. The transdermal drug delivery system F1 is having greater % drug release. Formulation F6 having less drug release capacity than other formulations. The formulation F6 shows better extended release up to 12 hrs when compared to other formulations. So it was concluded that the formulation F6 prepared by using Eudragit RS 100(1:2 ratio)is the better formulation for control release of drug up to 12 hrs of time. Results of the present study encouraged that the Diltiazem HCl with Eudragit RS 100 transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized. it is clearly indicated that the Diltiazem HCl transdermal patches containing Eudragit RS 100 in the ratio of 1:2 (F6) was the best formulation among the prepared patches.

Keywords: Transdermal, Diltiazem, Formulation and Development.

Introduction*:* With the advent of new era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms,though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex processinvolving extensive efforts. This review article describes the methods of preparation of different types of transdermal patches viz., matrix patches, reservoir type, membrane matrix hybrid patches, drug-in- adhesive patches and micro reservoir patches. In addition, the various methods of evaluation of transdermal dosage form have also been reviewed.

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Advantages of Transdermal patches

- Provide relatively steady and sustained drug concentration in plasma.
- Variability due to factors such as pH intestinal motility, food intake, etc, which make vast difference in the bioavailability of the drugs given through oral route, are notexistent.
- The hepatic first pass metabolism isavoided.

Disadvantages of Transdermal patches

- Can be used only for drugs, which require very small plasma concentrations for action.
- Local irritation and arrythmia are possible. Enzymes in epidermis or derived from microorganisms present on the skin may denature the drugs.

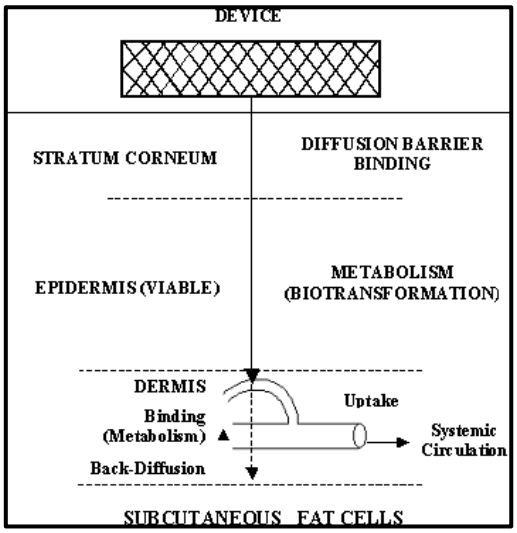

Fig.1 Events of drug transport across skin

Methodology

Materials: Diltiazem hydrochloride was obtained as a gift sample from Glenmark pharmaceuticals, Pithampur, Dhar (MP). Other excipients are procured from SdFine-chem. limited (Mumbai). All the reagents used in the study were of analytical grade and the solutions were prepared using double distilled water.

Method

Description: Diltiazem HCl was physically examined for colour and odour etc.

Solubility: The solubility of the selected drug was determined in distilled water and phosphate buffer of pH 7.4 using standard method.

Melting Point: Fine powder of Diltiazem HCl was filled in glass capillary tube (previously sealed at one end) and kept in melting point apparatus. The melting point was found.

Compatibility Studies: Compatibility with Drug and Polymers was confirmed by carrying out IR studies.

Estimation of Diltiazem HCl: A Spectrophotometric method based on the measurement of extinction at 236 nm in phosphate buffer of pH 7.4 was used for the estimation of Diltiazem HCl.

Preparation of Transdermalpatches: The trasdermal patches were prepared by solvent evaporation method. Different polymers (Eudragit RS 100, Eudragit RL 100 and HPMC) alone and in combination were accurately weighed and dissolved in 20 ml solvent. Known volume of Dibutyl phalate was used asplasticizer and oleic acid used as permission enhancer and mixed thoroughly with help of magnetic stirrer.120mg of drug was dissolved in the solution and mixed for 10mins. The resulted uniform solution was poured into petri dish and kept for the evaporation after 24hrs a dried film were out and stored in desiccators.

Evaluation of Transdermalpatches

Uniformity ofweight: This was done by weighing five different patches of individual batch taking the uniform size at random and calculating the average weight of 3. The tests were performed on films which were dried at 60oC for 4h prior to testing.

Thickness of the patch: The thickness of the patch was assessed by using digital vernier caliper at different points of the patch. From each formulation three randomly selected patches were used. The average value for thickness of a single patch was determined.

Moisture content: The patches were weighed individually and kept in a desiccator containing calcium chloride at 37oC for 24 hrs. The final weight was noted when there was no change in the weight.

Table 1: Formula for Diltiazem hydrochloride patch

Ingredients	**Formulation Code**						
	F1	F2	F3	F4	F5	F6	F7
Diltiazem HCl (mg)	120	120	120	120	120	120	120
HPMC (mg)	120	240	-	-	-	-	-
RL 100 (mg)	-	-	120	240	-	-	120
RS 100 (mg)	-	-	-	-	120	40	120
Oleic acid (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Dichloro methane (ml)	10	10	20	20	20	20	20
Ethanol (ml)	10	10	-	-	-	-	-
Dibutylphalate (%)	15	15	15	15	15	15	15

Moisture uptake: A weighed film kept in desiccator at 40oC for 24h was taken out and exposed to relative humidity of 93%RH (saturated solution of Potassium bromide) in a desiccator at room temperature then the weights were measured periodically to constant weights.

Determination of tensile strength: The tensile strength is determined as stretching force applied to the sample at which point it breaks. These measurements were

performed on a dumbbell shaped specimen. A specified weight was hung from the film through the specimen such that a pulling force was created. The force applied on the load cell of the apparatus was measured in kg/cm2.

Folding Endurance: This was determined by repeatedly folding one film 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.

Drug content determination: The patches at 1Cm2 were cut and added to a beaker containing 100ml of Phosphate buffered solution of pH 7.4. The medium was stirred with a magnetic bead for 5hrs. The solution was later filtered and analyzed for drug content with proper dilution at 236 nm spectrophotometrically.

Water vapour transmission (WVT) rate: The film was fixed over the brim of a glass vial, containing 3 g of fused calcium chloride as desiccant, with an adhesive tape. The vial was weighed and kept in desiccator containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs intervals for a period of 72 hrs. The WVT was calculated by taking the difference in the weight of the patches before and at regular intervals of 24 hrs.

In-vitro drug release studies: The fabricated film was placed on the semi permeable membrane and attached 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 7.4 at 37±10C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analyzed for drug content using UV spectrophotometer at 236 nm.

Result and Discussion

Description: Diltiazem HCl was physically examined for colour. It is white amorphous powder.

Solubility: Diltiazem HCl was freely soluble in water, methanol, acetone and other organic solvents.

Melting point: The melting point of Diltiazem HCl was found to be 2100C.

Compatibility Studies: The results of compatibility studies are shown in Fig 14 to 21.

Prepartion of standard calibration curve of Diltiazem HCl

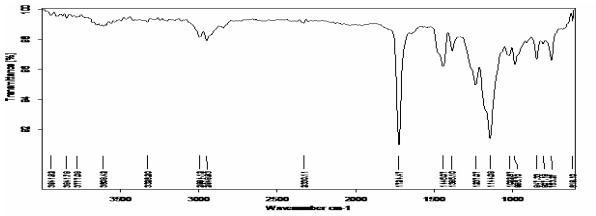

Fig. 2: IR Spectrum of Diltiazem HCl

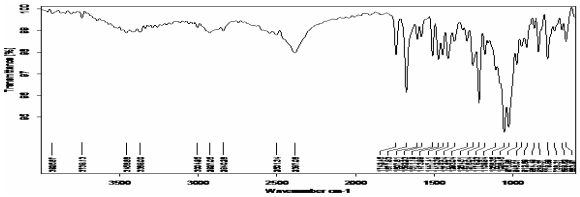

Fig. 3: IR spectrum of HPMCK4M

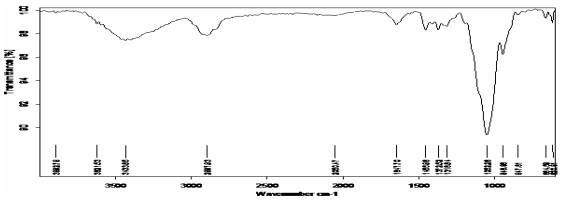

Fig. 4: IR spectrum of Diltiazem HCl and HPMC K4M

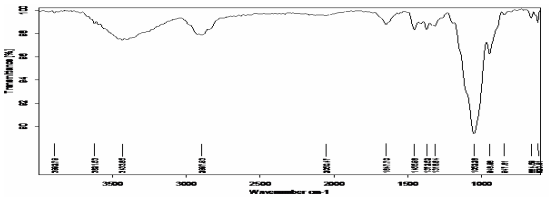

Fig. 5: IR spectrum of Eudragit RL 100

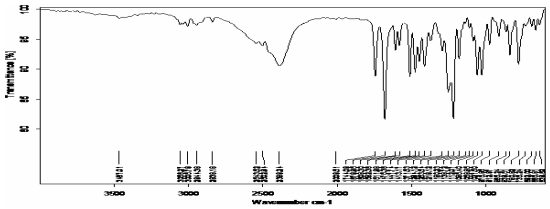

Fig.6: IR spectrum of Eudragit RS 100

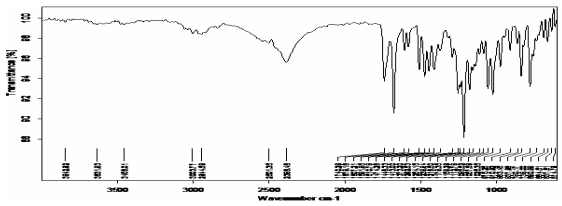

Fig. 7: IR Spectrum of Eudragit RS 100

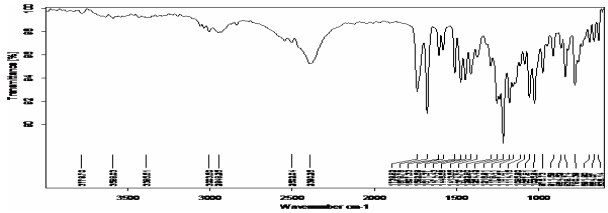

Fig. 8: IR spectrum Diltiazem HCl Eudragit RS 100 and Eudragit RL 100

Table 2: Weigt Variation

S. No.	Code	Trial 1 (mg)	Trial 2 (mg)	Trial 3 (mg)	Avg (mg)
1	F1	151	156	153	153.3±2.51
2	F2	240	244	244	242.6±2.30
3	F3	167	164	168	166.3±2.08
4	F4	238	239	238	238.5±0.57
5	F5	170	169	175	171.3±3.21
6	F6	222	228	229	226.3±3.78
7	F7	80	183	181	181.4±1.52

Table 3: Thickness Uniformity

S. No.	Code	Trial 1(mm)	Trial 2(mm)	Trial 3(mm)	Avg (mm)
1	F1	0.16	0.16	0.16	0.16±0.00
2	F2	0.19	0.18	0.19	0.185±0.005
3	F3	0.13	0.13	0.14	0.133±0.005
4	F4	0.19	0.2	0.21	0.2±0.01
5	F5	0.16	0.17	0.17	0.166±0.005
6	F6	0.21	0.22	0.23	0.22±0.01
7	F7	0.21	0.2	0.21	0.206±0.005

Table 4: Drug Content and water vapor transmission rate

S. No.	Code	Drug content (%)	Water vapor transmission rate ($gm/cm^2/hr)X10^{-4}$
1	F1	97.68	3.99
2	F2	96.59	4.21
3	F3	96.86	1.784
4	F4	95.77	1.59
5	F5	97.15	3.22
6	F6	98.67	3.7
7	F7	98.11	2.5

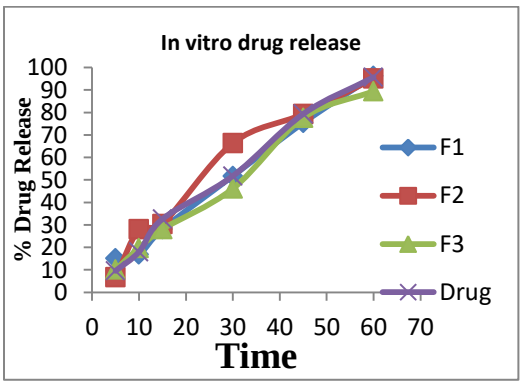

Fig 9: Comparison of drug release profile of transdermal patch of F1, F2, F3

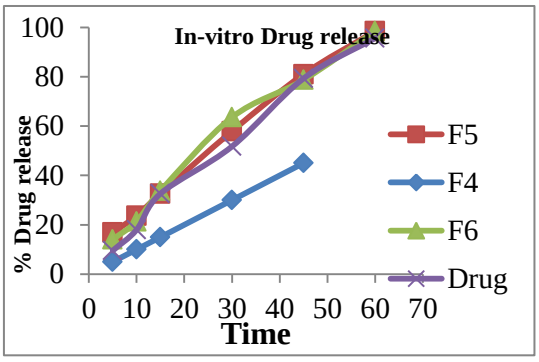

Fig 10: Comparison of drug release profile of transdermal patch of F4,F5,F6 Batches

Conclusion: The preformulation studies involving description, solubility, melting point, of the drug were found to be comparable with the standard.Based on all these factors the transdermal drug delivery system F1 is having greater % drug release. Formulation F6 having less drug release capacity than other formulations. The formulation F6 shows better extended release up to 12 hrs when compared to other formulations.So it was concluded that the formulation F6 prepared by using Eudragit RS 100(1:2 ratio)is the better formulation for

control release of drug up to 12 hrs of time. However the in vitro drug release of the best formulation F6 follows first order kinetics and the mechanism of diffusion. Results of the present study encouraged that the Diltiazem HCl with Eudragit RS 100 transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized.

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