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FORMULATION DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCHES OF NISOLDIPINE

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ABSTRACT

The purpose of this research was to develop matrix type transdermal therapeutic system containing Nisoldipine with different ratios of hydrophilic and hydrophobic polymeric concentration by the solvent evaporation technique. The prepared patched showed satisfactory physiochemical characteristics of weight uniformity, thickness, folding endurance, moisture absorption for stability of the formulation and drug content were uniform in all patches. In vitro study done by using Franz diffusion cell having cellophane membrane to determine the amount of drug present in the formulated patch. In different formulation on the basis of present study formulation F5 show satisfactory drug release pattern.

Key Words:- Nisoldipine, Transdermal patches, *In vitro* skin permeation.

INTRODUCTION

Novel drug delivery is geared towards developing friendly dosage forms of various formulations with the ultimate aim of increasing their dosing convenience to the patient. The NDDS may involve a new dosage form e.g., from thrice a day dosage to once a day dosage form or developing a transdermal patch in place of injections. Today, about 74% of drugs are taken orally and are found not to be as effective as desired (Chong S and Fung HL, 1989). Thus, various forms of NDDS such as transdermal delivery systems, controlled release systems, transmucosal delivery systems etc. emerged. In addition, because transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing, it is generally accepted that they offer improved patient compliance. Transdermal patch is a device for delivering the therapeutic substances through the skin for systemic effect at predetermined and controlled rate; comprising of backing membrane, drug incorporated into matrix, release liner and with/without rate controlling membrane (Walter Kennath A, 2000).

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Desirable features for transdermal patches

1. Composition relatively in variant in use.
2. System size reasonable.
3. Defined site for application.
4. Application technique highly reproducible.
5. Delivery is (typically) zero order.
6. Delivery is efficient (Walter Kennath A, 2000).

Nisoldipine is a second generation long acting dihydropyridine calcium channel blocker having a 10 fold vascular selectivity than felodipine, isradipine, nicardipine and 100 fold selectivity than amlodipine and nifedipine (Nepolean R *et al.*, 2012). The oral bioavailability of Nisoldipine was highly reduced (3.9 – 8.4%) due to first pass metabolism in liver and the pre-systemic metabolism in gut wall. Nisoldipine was chosen as a model drug for study since it possess near ideal characteristics that drug

must have in formulating drug delivery system such as low molecular weight, high lipid solubility, effective in low plasma concentration as well as high degree first pass effect. It also means multiple administrations with subsequent lack of patient compliance.

MATERIALS AND METHODS

Material

Nisoldipine was obtained as a gift sample from hetro labs, EC (Ethyl- Cellulose), PVP, PEG-400 and Tween 80, Span 80 other excipient used in the processing of manufacture of the patches, is purchased from MS Traders. All the other reagents or solvents used were of analytical grade.

Methods

Preparation of drug containing polymer matrices Drug loaded polymer patches were prepared by solvent evaporation technique. The drug matrix was prepared by PVP: EC in different ratio. The polymer in different ratios was dissolved in chloroform. Nisoldipine dissolved in ethanol and slowly added in polymer solution and mixed thoroughly to obtain a uniform solution, PEG-400 as a plasticizer was added and mixed. Films were casted by placing this solution on desired size flat Teflon plates allow evaporating the solvent for 24 hrs (Arora P and Mukherjee B, 2000).

Preformulation

Partition coefficient determination Partition coefficient is a measurement of drug's lipophilicity and its ability to cross cell membrane. Partition coefficient of Nisoldipine was determined at 37±0.5^{o}C by taking 10 ml of octanol which was saturated with 10 ml of phosphate buffer (pH7.4) by stirring with externally driven magnetic stirrer. After stirring the system remain undisturbed for half an hour. About 10 mg of drug was added to this solution and was shaken on wrist action mechanical stirrer. Two layers were separate through separating funnel and filtered through Whatman grade filter, and the amount of Nisoldipine solubilized, was determined by measuring the absorbance at 248 nm against reagent blank through double beam UV/Vis spectrophotometer (Shimadzu 1601-A) in both the solution. Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in phosphate buffer (pH 7.4) and the value were reported as log P6.

$$K_O/W = \frac{\text{Concentration of drug in non-aqueous phase}}{\text{Concentration of drug in aqueous phase}}$$

Drug-Excipient interaction study

The drug–excipient interaction study was performed using silica gel coated TLC (Thin Layer Chromatography) plates and a mixture of given volume of chloroform-methanol-acetone-formic acid (7.5:1.5:0. 5:0.03) as a mobile phase. The TLC plates were prepared using slurry of silica-G. The prepared plates were activated at 110^{o}C for 30 min. On the activated plates, 2µL of each solution in methanol of Nisoldipine containing different experimental ratio of excipient, that is, PVP, EC, were applied. The plates were dried in a stream of warm air for 10 min and then placed in contact with iodine vapours. The plates were heated at 110^{o}C for 15 min. The Rf values were calculated from the chromatogram obtained (Shivaraj A *et al*., 2010).

Permeation study of pure drug

The In vitro drug release experiment was carried out by using fabricated Franz diffusion cell. The treated rat skin was cut into desired size and clamped between the receptor and donor compartments. The receptor compartment was filled with 13.2 ml of diffusion medium (Phosphate buffer pH 7.4) through sampling port taking care to remove all the air bubbles. The contents were stirred at about 500 rpm by externally driven, teflon coated small magnetic bead to keep them well mixed. In order to attain 32 ± 0.5^{o}C at the skin surface, receptor compartment was maintained at 37.5^{o}C. Accurately weighed 10 mg of Nisoldipine (with suitable solvents and permeation enhancers) was placed on the membrane. At suitable intervals, aliquots 3ml were collected at present time , then determined by measuring the absorbance at 248 nm using a double beam UV spectrophotometer (Shimadzu 1601-A). The diffusion medium of the same volume 3ml, which was pre warmed at 37^{o} C, was then replaced into the diffusion cell. Duration of the experiment was 24 hrs. The experiments were performed in triplicate (n=3) and mean value was used to calculate the permeability coefficient. The amount of drug diffused was calculated from absorbance (Shivaraj A *et al*., 2010).

EVALUATION

Physical Evaluation of Transdermal Patch

A. Thickness measurement

The thickness of the drug containing polymer matrix was determined by measuring the thickness of the whole patches. The average thickness of drug containing polymer matrix was determined at four points using vernier caliper.

B. Weight uniformity

The prepared patches dried at 60°C for 4 hrs before testing. A specified area of patch was cut in

different parts of the patches and weight in digital balance. The average weight and standard deviation values calculated from the individual weights.

C. Folding endurance

A strip of specific area was cut and repeatedly folded 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 the folding endurance.

D. Moisture content

The prepared films were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hrs. The films were weighed again and again individually until it showed a constant weight. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight. A small amount of moisture in patch type formulations helps maintain stability and prevents the formation of a dried and brittle film. A greater amount, however, can lead to microbial contamination during storage. The moisture content is determined by variations in the water content of the dried film and un-dried film.

Percent moisture content is determined as follows.

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

E. Moisture uptake

A weighed film was kept in desiccators at normal room temperature for 24 hrs was taken out and exposed to 84% relative humidity (saturated solution of potassium chloride) in desiccators 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. This study can predict the moisture-absorbing capacity of a particular type of patch at various humidity levels. Little moisture uptake indicates the stability of the formulation. A good amount of moisture uptake indicates bulkiness of the formulation and the chance of microbial growth.

$$\text{Percentage moisture uptake} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

F. Drug contents uniformity

A specified area of patch was dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with UV method.

G. Percentage elongation break test

The percentage elongation break test was determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula:

$$\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100$$

Where, L1 is the final length of each strip and L2 is the initial length of each strip (Arora P *et al.*, 2000).

In vitro drug permeation study with different formulation

The In vitro permeation studies were conducted using fabricated Franz diffusion Cell. The treated rat skin was cut into desired size and placed between the receptor and donor compartments the diffusion cell. The fabricated patch was placed over the membrane. The donor compartment was placed on the receptor compartment containing phosphate buffer pH 7.4 maintaining at 37 ± 0.5^0C.

The entire assembly was kept on magnetic stirrer[6]. The solution in the receiver compartment was continuously stirrer with magnetic beads with about 500 rpm during the experiment. The amount the drug permeated through membrane was determined by withdrawing 2 ml of sample at predetermined time interval and replacing them with an equal volume of buffer. The withdrawal samples were diluted 10 times and filtered through filter paper (Whatman R 41). Absorbance of the sample was measured at 248 nm taking phosphate buffer as the blank. Drug absorbances were determined by the standard curve of Nisoldipine in phosphate buffer (pH7.4). The amount of drug permeated per square centimeter at each time interval was calculated from the calibration curve. The mean cumulative percentage of the drug permeation through total patch area was plotted against time (Vijayan V *et al*., 2010; Patel JH *et al*., 2009).

Table 1. Formulation of transdermal patches

Ingredient	F1	F2	F3	F4	F5
Nisoldipine	30	30	30	30	30
Ethyl Cellulose	500	400	300	200	100
PVP K30	100	200	300	400	500
Tween-80	6ml	6ml	6ml	6ml	6ml
PEG 400	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml
Chloroform: Alcohol	10ml	10ml	10ml	10ml	10ml

Table 2. Partition coefficient of drug in PBS 7.4

Partition coefficient of drug	Solvent system	Log p Values
Nisoldipine	Phosphate buffer: n-octanol	3.87 ± 0.03

Table 3. Partition coefficient of drug in skin

Partition coefficient of drug	Solvent system	Log p Values
Nisoldipine	Phosphate buffer: skin	3.85±0.04

Table 4. Rfvalue of Nisoldipine alone and with excipients

Sl. No	Sample	Initial Rf value	Rfvalue after 2 week
1	Drug	0.74±0.03	0.75±0.025
2	Drug+EC	0.72±0.13	0.74±0.09
3	Drug+PVP	0.73±0.06	0.74±0.10
4	Drug+All excipient	0.74±0.12	0.73±0.15

Table 5. Physiochemical characterization of transdermal patches

Parameter	F1	F2	F3	F4	F5
Thickness(µm)	52±10	61±10	54±10	65±10	55±15
Weight variation (mg)	115±2.13	115±2.13	111±2.53	109±3.0 5	95±2.07
Folding Endurance	59±2.8	55±3.6	55±3.6	49±3.2	45±2.8
Percentage Moisture Content (%)	1.035±0.32	1.113±0..35	1.096±0.14	1.252 ±0.22	1.481±0.24
Percentage Moisture Uptake (%)	1.112±0.25	0.994±0.15	1.028±0.27	1.118±0.22	1.124±0.23
Drug Content	89.21±0.24	84.61±0.19	79.44±0.34	88.92±0.16	94.21±0.21
Percentage Elongation break (%)	92.4	92.3	85.5	87. 1	113.1
Percentage cumulative amt. permeation (%)	68.57	74.19	69.86	84.92	90.28

Table 6. Curve fitting data for the release rate profile of formulation F5

Model	r^2 value
Krosmeyers – peppas	0.4278
Zero order	0.7221
First order	0.3437
Higuchi matrix	0.9981
Hixson Crowel	0.1501

Fig 1. Percentage moisture content

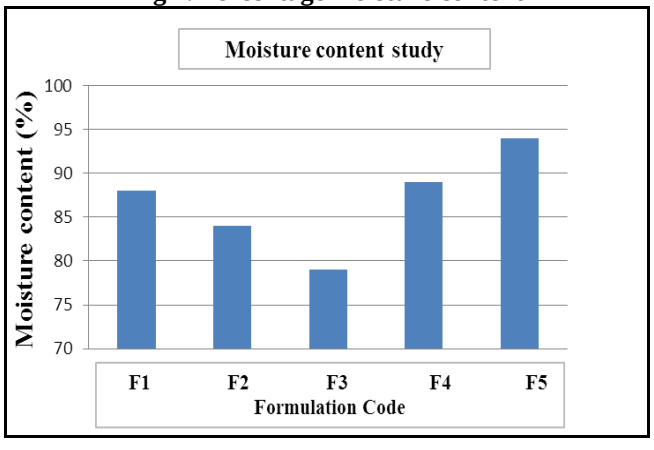


Fig 2. Moisture uptake study

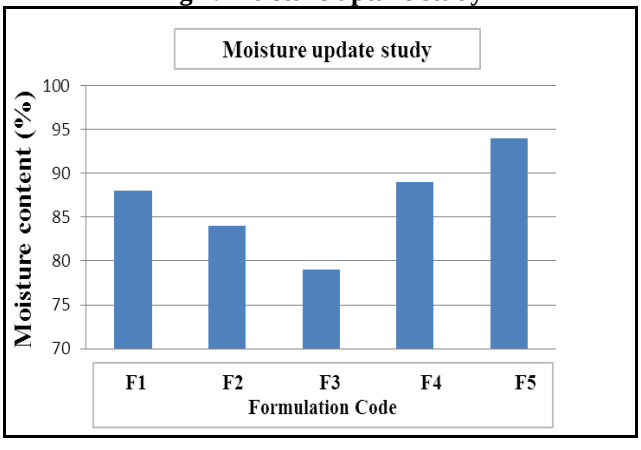


Fig 3. Percentage drug content

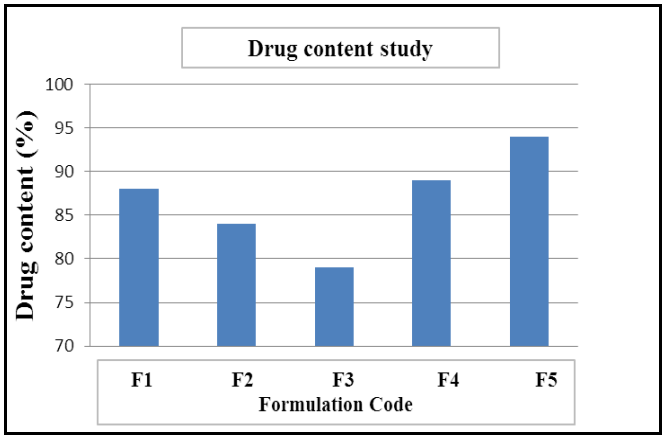
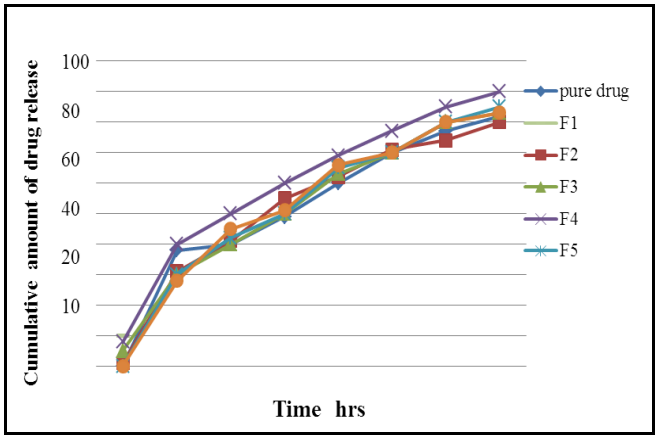


Fig 4. In vitro drug permeation profile of different formulation



RESULTS AND DISCUSSION

In the present work efforts have been made to prepare transdermal drug delivery system of Nisoldipine, EC and PVP, using polyethylene glycol as a plasticizer by solvent casting technique. The selection of polymer combinations produces clear, smooth, uniform, substantive, flexible and desired thickness film for the transdermal drug delivery systems of Nisoldipine. The prepared formulation were evaluated for different physico-chemical characteristics such as thickness, folding endurance, drug content, percent moisture absorption, percentage moisture loss and weight uniformity. The release characteristics of the formulation were studied in in-vitro conditions. In vitro permeation studies were carried out in phosphate buffer (pH 7.4) for 24 hours. The partition coefficient of the Nisoldipine was found to be 3.87, After 24 hrs. 71.25 % drug was permeated through skin. The thickness of the patches varied from 52 to 65µm. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible result. As the concentration of PVP and Ethyl cellulose increase, moisture content of patches was also increase. Formulation F5 (1.481±0.24) absorbed highest amount of moisture which also revealed its high hydrophilicity and formulation F1 (1.096±0.14) absorb least amount of moisture. The folding endurance was measured manually; films were folded 59 times maximum in formulation F1and if the film shows any cracks it was taken as end point. The folding endurance was better in F1 formulation. As the concentration of PVP and Ethyl cellulose increase, moisture uptake of patches was also increase. The highest moisture absorption was found in the formulation F5 and lowest value of moisture absorption was found in the formulation F1. The drug content uniformity of the prepared formulation have shown that the process used to prepared the transdermal film in this study was capable of giving film with uniform drug content. The result of drug content indicates that drug is uniformly dispersed in formulation. In vitro drug permeation studies were carried out for the different formulations using Franz diffusion cell. The medicated films showed drug release study in % cumulative release. The relationship can be established as F5 >F4 > F2>F3>F1 Thus, by varying amount of polymer in film, percent release can be varied. Drug-polymer affinity can be major factor that control release of drug from formulation. Maximum percentage of drug release (i.e. 90.28%) was observed with formulation F5 and the minimum (i.e. 68.57%) was found with formulation F1. The addition of hydrophilic components such as PVP into the formulation tends to enhance its release-rate constants. This outcome can be attributed to the leaching of the soluble component, which leads to the formation of pores and thus a decrease in the mean diffusion path length of drug molecules to release into the dissolution medium the result is higher dissolution rates. Substances such as PVP act as antinucleating agents that retard the crystallization of a drug. Thus they play a significant role in improving the solubility of a drug in the matrix by sustaining the drug in an amorphous form so that it undergoes rapid solubilization by penetration of the dissolution medium.

CONCLUSION

The prepared transdermal drug delivery system of Nisoldipine using different ratios of polymers such as EC and PVP had shown good promising results for all the evaluated parameters. Based on the In vitro drug release and drug content result, formulation F5 was concluded as an optimized formulation, which shows its higher percentage of drug release.

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