

# Effect of additives and solvents on inhibition of crystallization in transdermal patches containing repaglinide

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## ABSTRACT

Repaglinide is used as antidiabetic drug it has half-life of 1 hour and bioavailability in the body is 56% due to first pass metabolism. The total daily dose of Repaglinide is 16 mg (e.g., 4 mg four times daily depending on meal patterns), hence it required frequent dosing. Because of its low half-life repaglinide has to be administered more frequently to maintain the plasma levels. This may lead to reduction in patient compliance or sometimes the patient may fail to take the drug. Therefore a modified dosage form of Repaglinide is preferred over a conventional dosage form. Hence in our present work we planned to formulate *Transdermal Patches of Repaglinide*. The most commonly encountered problem in transdermal patches is *crystal growth* during the process of drying the patch or during its storage. This work was aimed at finding out the effects of additives on crystal growth inhibition. Various trials were conducted by using different formulations such as placebo trials by following single blinded technique using HPMC and HPC, and povidone as polymers, various solvents and plasticizers. Seventeen formulations (F-1 to F-17) were prepared by using different solvents and polymers to observe the crystallization on patches and finally the most preferred formulation which inhibits the crystallization has been selected.

## KEY WORDS:

Repaglinide patche, polymers, crystallization, plasticizers, solvents

## INTRODUCTION:<sup>1</sup>

At present, the most common form of delivery of drugs is the oral route. New drug delivery systems are also essential for the delivery of novel, genetically engineered pharmaceuticals to their site of action, without causing significant biological inactivation. One of the methods most often utilized is transdermal drug delivery system.

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drugs through the skin, at a controlled rate to the systemic circulation. Designing of transdermal delivery system requires an understanding of the permeation behavior of drug through the skin.

Some of the factors responsible for drug permeability include –

- The amount of active agent accumulated in the different strata of the skin
- The flux through the skin into systemic circulation & the mechanism of penetration.

Percutaneous absorption involves passive diffusion of substances through the skin.

The mechanism of permeation involves –

- ✓ Transepidermal absorption (passage through the epidermis).
- ✓ Transfollicular / shunt pathway absorption (diffusion through shunts, particularly those offered by widely distributed hair follicles and eccrine glands).

## BASIC COMPONENTS OF TRANSDERMAL DEVICES –

- Transdermal drug delivery systems are designed to support the passage of drug substances from the surface of skin, through its various layers, and into the systemic circulation.
- The components of transdermal devices include –
  - ✓ Polymer matrix or matrices – that reserve & regulate the release of drug
  - ✓ The drug
  - ✓ Permeation enhancers
  - ✓ Adhesive - to register the preparation topically.
  - ✓ Backing membrane

## APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Four different approaches have been utilized to obtain transdermal drug delivery systems:

1. Membrane permeation – Controlled systems

2. Adhesive dispersion- type systems
3. Matrix diffusion controlled systems
4. Microreservoir type or microsealed dissolution controlled systems

The present work was aimed at formulating transdermal patches of Repaglinide using different polymers. The composition of these formulations will be selected by using trial and error technique. To study the effect of various factors like drug polymer ratio, drug plasticizer ratio, and effect of various solvents on inhibiting the crystal growth on transdermal patches.

#### Materials and Methods:

Sno	Materials	
1	Repaglinide	Drug
2	HPMC,HPC	Polymer
3	Povidone	Polymer
4	Polyethylene glycol	Plasticizer
5	Methanol, Ethanol,Dichloromethane,Chloroform	Solvent

#### METHOD<sup>2,3,4</sup>

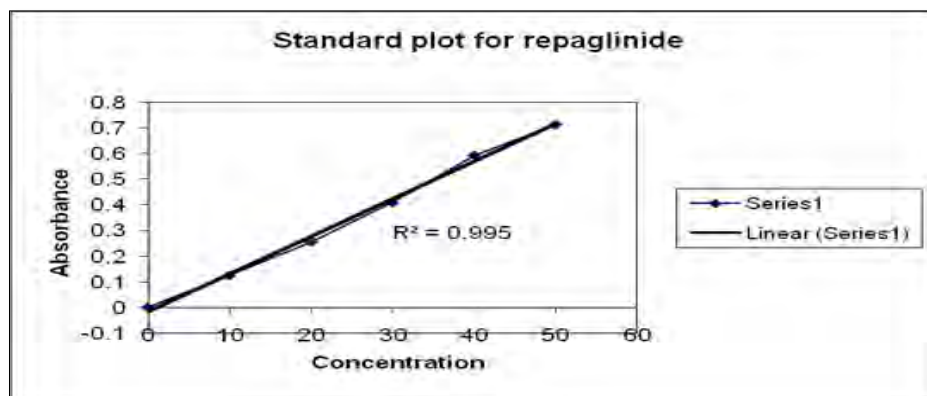
Drug-loaded matrix-type transdermal patches of Repaglinide were prepared by using solvent casting method. A Petri dish with a total area of 81.67 cm<sup>2</sup> was used and polymers were accurately weighed and dissolved in the selected solvent or a combination of solvents based on the formula and kept aside to form clear solution. Drug was dissolved in the above solution and mixed until clear solution was obtained, Plasticizer was added and the entire solution containing in a beaker was stirred on the magnetic stirrer for 20 min. The resulted uniform and clear solution was cast on the petri dish, and dried at room temperature for 24 Hours. An inverted funnel was placed over the petri dish to prevent fast evaporation of the solvent, after 24 Hours, the dried patches were taken out and stored in a desiccator for further studies.

#### RESULTS AND DISCUSSION

##### Standard plot

Various concentrations i.e., 0%, 10%, 20%, 30%, 40% and 50% of Repaglinide were prepared by using methanol as solvent. The absorbance was measured with the help of a UV-double beam spectrophotometer and was noted. With the values a standard Curve was plotted at  $\lambda_{max}$  288nm.

Fig 1: Standard plot for Repaglinide



From the above scatted graph  $R^2 = 0.995$ ,

The Coefficient of determination was between 0 to 1 and hence the observed values were in straight line.

Various trails were conducted by using different formulation such as placebo trails by following single blinded technique using HPMC and HPC, and povidone as polymers, various solvents and plasticizers. Seventeen formulation (F-1 to F-17) were prepared by differnts solvents and polymers to observe the crystallization.

TABLE 1: PLACEBO TRIALS FOR HPMC

Patches	HPMC K100M	HPMC K15M	PEG	METHANOL+DICHLOROMETHANE
P1	400mg	-	0.08 ml	20+20ml
P2	-	400mg	0.08 ml	20+20ml

TABLE 2: PLACEBO TRIALS FOR HPC

Patches	HPC LXF	HPC HXF	PEG	METHANOL	ETHANOL
P3	400	-	0.08	40	-
P4	-	200	0.08	40	-
P5	400	-	0.08	-	40

While doing placebo trails a total of five formulations were made namely P1 using HPMC K100M 400mg, PEG 0.08ml, methanol 20ml and dichloromethane 20ml respectively. In patch P2 HPMC K15M 400mg, PEG 0.08ml, methanol 20ml and dichloromethane 20ml each. In trails P3-P5 HPC Polymer was used and solvent combination was changed. In P3 HPC LXF 400mg, methanol 40 ml .In P4 HPC HXF 200 mg and methanol 40 ml, in P5 HPC LXF 400mg, ethanol 40 ml were used.

TABLE 3: PRELIMINARY PATCHES

	F-1	F-2	F-3	F-4
API	0.654	0.654	0.654	0.654
HPMC K15M	400	-	-	-
POVIDONE	-	-	-	400
HPC LXF	-	400	400	-
PEG	0.08	0.08	0.08	0.08
METHANOL	20	40	-	20
ETHANOL	-	-	40	-
DICHLOROMETHANE	20	-	-	20

A total of four formulations were prepared. In all the formulations PEG and drug were common 0.08ml and 0.654 mg respectively. In F1 HPMC K 15M 400mg whereas in F2 and F3 HPC LXF 400mg, F4 Povidone 400 mg polymers were used. In F1 and F4 methanol 20ml and dichloromethane 20ml each were added. In F2 Methanol 40 ml, In F3 Ethanol 40 ml was used in making of preliminary patches.

**TABLE 4: FORMULATIONS TO OBSERVE EFFECT OF SOLVENTS ON CRYSTALLIZATION**

	<b>F-5</b>	<b>F-6</b>	<b>F-7</b>	<b>F-8</b>
<b>API</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>
<b>HPMC</b>	<b>400</b>	<b>400</b>	<b>400</b>	<b>400</b>
<b>PEG</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>
<b>METHANOL</b>	<b>40</b>	-	-	-
<b>DICHLOROMETHANE</b>	-	<b>40</b>	-	-
<b>CHLOROFORM</b>	-	-	<b>40</b>	-
<b>ETHANOL+CHLOROFORM</b>	-	-	-	<b>20+20</b>

While observing the effect of solvents on crystallization a total of four formulations were made from F5-F8. In all the formulations PEG, HPMC K15M and drug were common 0.08ml, 400mg and 0.654 mg respectively. Here solvent is varied in F5 methanol 40 ml, In F6 dichloromethane 40ml, In F7 Chloroform 40 ml and in F8 ethanol and chloroform 20 ml each were added.

**TABLE 6: FORMULATIONS TO OBSERVE EFFECT OF POLYMERS ON CRYSTALLIZATION**

	<b>F-9</b>	<b>F-10</b>	<b>F-11</b>	<b>F-12</b>	<b>F-13</b>	<b>F-14</b>	<b>F-15</b>	<b>F-16</b>	<b>F-17</b>
<b>API</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>	<b>0.654</b>
<b>HPMC + K 15M</b>	<b>200</b>	<b>300</b>	<b>200</b>	<b>100</b>	<b>200</b>	<b>210</b>	<b>180</b>	<b>220</b>	<b>190</b>
<b>POVIDONE</b>	-	-	-	-	<b>200</b>	<b>190</b>	<b>220</b>	<b>180</b>	<b>210</b>
<b>HPC+LXF</b>	<b>200</b>	<b>100</b>	<b>50</b>	<b>100</b>	-	-	-	-	-
<b>PEG</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>	<b>0.08</b>
<b>METHANOL</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>
<b>DICHLOROMETHANE</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>

While observing the effect of polymers on crystallization a total of nine formulations were made F9-F17. In all the formulations of PEG, methanol, dichloromethane and drug were common 0.08ml, 20ml, 20ml, 0.654 mg respectively. Here in each formulation a combination of two polymers were used. From F9-F12 HPMC K15M and HPC LXF in absence of Povidone were made in F9 200mg of HPMC K15M and HPC LXF were used. In F10 HPMC K15M 300mg, HPC LXF 100mg. In F11 HPMC K15M 200mg, HPC LXF 50mg. In F12 HPMC K15M 100mg, HPC LXF 100mg. Whereas from F 13-17 absence of HPC LXF, combination of HPMC K15M and Povidone were used. In F13 HPMC K15M 200mg, Povidone 200mg. In F14 HPMC K15M 210mg, Povidone 190mg. In F15 HPMC K15M 180mg, Povidone 220mg. In F16 HPMC K15M 220mg, Povidone 180mg. In F17 HPMC K15M 190mg, Povidone 210mg were made.



FIG-1  
FORMULA 5



FIG-2  
FORMULA 10



FIG-3  
FORMULA 8



FIG-4  
FORMULA 14

Coming to the inference from the above figures, in fig-1 patch was formed but network like crystals and slight yellow coloration was seen. In fig-2 uniform patch was formed but crystals were observed no discoloration. In fig-3 patch was not uniform very brittle in nature and yellow colour at edges. In fig -4 patch was clear, uniform, no crystals and no discoloration. Thus from all the above formulas observed fig-4 formula 14 was selected. *F-14 which contains 190 mg of povidone 210 mg (HPMC K15M) and absence of (HPC LXF) and has shown no crystallization with a clear and uniform patch.*

### CONCLUSION

Initially Placebo Trials (P1 to P5) were performed to determine the required polymer and plasticizer concentrations in order to obtain a patch. In the placebo trials, HPMC and HPC polymers were tested. Among the two placebo patches with HPMC (P1 & P2), both were very brittle. Among formulations P3 to P5 which has HPC, the solution of P4 was highly viscous with many globules were as with the formulation P5, patch was not obtained on drying.

From formulations F-5 to F-8, were formulated to observe the effect of solvent on crystallization inhibition. The patches with chloroform were brittle and the patch with dichloromethane has shown slight yellowish coloration of the patch. The patch with methanol has shown no crystallization or color formation.

From formulations F-9 to F-19, were formulated to find out the effect of polymers, F-9, F-10, F-11 and F-12 had a combination of HPMC and HPC with a combination of methanol and Dichloromethane as solvent in 1:1 ratio. All of them has shown crystallization. F-13, F-14, F-15, F-16 and F-17 were formulated in various combinations of HPMC with povidone K 30. Among these F-13 has shown incomplete drying whereas with patches F-15, F-16 and F-17 patch was formed without any crystals but was not clear. *F-14 has shown no crystallization with a clear and uniform patch.*

Hence from the above discussion it can be concluded that *solvents has no considerable effect in inhibition of crystal growth in the repaglinide patches whereas povidone has shown significant inhibition of crystal growth in crystallization.*

Thus in the present study the effect of additives was studied in inhibition of crystal growth on Repaglinide<sup>5,6,7</sup> patches and further continuation of work is promised

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