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FORMULATION DEVELOPMENT OF ROSUVASTATIN CALCIUM DRUG IN ADHESIVE TRANSDERMAL SYSTEM

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Keywords:

Rosuvastatin calcium, Drug- in-adhesive, % cumulative release, Peel adhesion strength, Tensile strength

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ABSTRACT: Current investigation was aimed at designing a Rosuvastatin calcium loaded drug- in- adhesive patch (DIAP) to overcome the problems associated with the daily oral administration of the drug. The patches were prepared by solvent casting method using acrylate emulsion polymers like Covinax 525-78, Mowinyl 461 and Novacryl PSR $3^{2,}$ which served as sustained release matrix polymer and adhesive. Methocel K100M was added as a solubilizer whereas propylene glycol (PG), labrasol, transcutol, and polyethylene glycol 400 (PEG400) were tried as permeation enhancers for the drug- in- adhesive film. The combination of Novacryl –PEG 400 and Novacryl-Transcutol was further optimized by 3^2 factorial design to study the effect of two independent variables *i.e.* concentration of solubilizer and permeation enhancer on responses *i.e.* % drug release, tensile strength and peel adhesion strength. The effect of the solubilizer and permeation enhancer on the final formulation was studied. The % cumulative release of drug at the end of 24 h was found to be between 90-93%. The formulations also show tensile strength in the range of 6-11 kg/cm^2 and peel adhesion strength of 14-16 N/25 mm. Hence the developed transdermal patch could be acceptable for transdermal use.

INTRODUCTION: Hyperlipidemia is a patho-logical condition where there is a presence of abnormally high concentration of fats (cholesterol, cholesterol esters, triglycerides and phospholipids) in the blood. The statins are a class of drugs that can reduce the endogenous synthesis of cholesterol and prevent the onset and the development of atherosclerosis, and are therefore used as an effective therapy against primary hyper-cholesterolemia [1-3]. The treatment of hyper-cholesterolemia is often long-lasting.

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In this case, it is very important that the plasma concentration of the drug is kept as steady as possible, and also the administration scheme be as simple as possible for the patient. Statins (also known as 3-hydroxy-3-methyl-glutaryl coenzyme A [HMG-CoA] reductase inhibitors) are generally recognized as the treatment of choice in patients with hypercholesterolemia because they are easy to use, effective, and well-tolerated.

A number of statins are on the market: atorvastatin (Lipitor and Torvast), fluvastatin (Lescol), lova-statin (Mevacor, Altocor, Altoprev), pitavastatin (Livalo, Pitava), pravastatin (Pravachol, Selektine, Lipostat), rosuvastatin (Crestor) and simvastatin (Zocor, Lipex). At present, these statin drugs are administrated orally on a daily basis. All statins are absorbed rapidly following oral administration, however several problems have been found

associated with the daily oral administration. For instance, atorvastatin provides a bio-availability not more than 14% and only about 5% of simvastatin enters into the general circulation. This is due to the first-pass metabolism in the liver and the clearance by the digestive system. Thus, increased dosages of statin drugs are usually used to obtain the expected therapeutic efficacy. The immediate-release formulations are reported to show nonlinear pharmacokinetics at doses greater than 20 mg. This may lead to increased risk of adverse effects, like dose-related musculoskeletal and hepatic toxicities.

Tank C *et al.,* 2015 prepared Fluvastatin sodium transdermal patch using polyacrylate based pressure-sensitive adhesive [4]. Bhaskar V *et al.,* 2016 developed and evaluated Simvastatin solid lipid nanoparticles loaded into transdermal patch [5]. Kaur R *et al.,* 2019 prepared Fluvastatin loaded nano-emulsion gel for treatment of osteoporosis [6].

Mendes M *et al.,* 2017 developed a monolithic drug-in-NLC-in-adhesive transdermal patch for codelivery of Olanzapine and Simvastatin [7]. Parhi R *et al.,* 2018 developed DIA patch of Simvastatin using acrylic adhesives such as DURO-TAK® 87-9301, DURO-TAK® 87-4287, DURO-TAK® 87-235A [8]. Anod V. H *et al.,* 2018, prepared Simvastatin transdermal films for the treatment of atherosclerosis by solvent evaporation technique [9].

Geevarghese RB *et al.,* 2018 developed RP-HPLC method for estimation of Rosuvastatin calcium from bulk and transdermal dosage form [10].

Transdermal drug delivery system is advantageous over other routes of administration in evading the first-pass metabolism by the liver, exempt from the impacts of the gastrointestinal fluids, provides controllable sustained effects, and reduces toxicity and side-effects leading to better therapeutic effect. Rosuvastatin calcium is a poorly water-soluble drug with only 20% oral bioavailability. The poor solubility of rosuvastatin calcium affects its dissolution rate and, in turn, its bioavailability. Owing to its poor oral bioavailability and good permeability (BCS Class II), a transdermal patch loaded with rosuvastatin calcium was developed. This transdermal system can be used as a better alternative for the treatment of hyper-cholesterolemia.

MATERIALS AND METHODS:

Materials: Rosuvastatin calcium was received as a gift sample from Cipla Ltd., Mumbai. Acrylate polymers Mowinyl 461 (Nippon Synthetic Chemical Industry Ltd), Novacryl PSR 32 (Omnova Solution Inc) and Covinax 525-78 (Franklin Adhesives and Polymers) were received as gift samples. These emulsion polymers were selected on the basis of pH, glass transition temperature (Tg), and solid content [11]. Acrylate polymers used as PSA typically have a Tg of -20 °C, preferably from -40 to-80 °C. This low Tg gives the PSA its soft, tacky properties. Transcutol CG USP/NF was received as a gift sample from Gattefosse SAS. Other chemicals and solvents used in the study were of analytical grade.

TABLE 1: COMPOSITION OF ROSUVASTATIN CALCIUM LOADED DIAP

Content	Formulation Code											
	CPG	MPG	NPG	CT	MT	NT	CL	ML	NL	CPEG400	MPEG 400	NPEG400
Rosuvastatin	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Covinax	0.8	-	-	0.8	-	-	0.8	-	-	0.8	-	-
Mowinyl	-	0.8	-	-	0.8	-	-	0.8		-	0.8	-
Novacryl	-	-	0.8	-	-	0.8	-	-	0.8	-	-	0.8
Propylene Glycol	0.27	0.27	0.27	-	-	-	-	-	-	-	-	-
Transcutol	-	-	-	0.18	0.18	0.18	-	-	-	-	-	-
Labrasol	-	-	-	-	-	-	0.18	0.18	0.18	-	-	-
PEG 400	-	-	-	-	-	-	-			0.27	0.27	0.27
Methocel K100M	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled Water .q.s	10	10	10	10	10	10	10	10	10	10	10	10

All weights are in grams

Formulation of Rosuvastatin Calcium Loaded Drug in Adhesive Patch: Drug in an adhesive patch (DIAP) were made from three different acrylate emulsion polymers Covinax, Mowinyl and Novacryl using different permeation enhancers like Propylene glycol (PG), Labrasol, Transcutol and

Polyethylene glycol 400. These polymers, when used alone, remained extremely tacky, and the films formed were difficult to remove from the mould. Replacing a part of the acrylate emulsion polymer with Methocel K100M improved the films casting property while still maintaining a good amount of tack property. The crystallization of drugs is reported in the case of transdermal systems. Several additives like Hydroxy propyl methylcellulose (HPMC), Polyvinyl pyrrolidine (PVP), *etc.* are known to inhibit crystallization by preventing crystal nucleation adsorption onto crystals or forming additive drug co-precipitates.

All these mechanisms can increase permeation and release profiles of drugs [12-14]. So, the addition of Methocel K100M served a dual purpose. Weighed quantities of the drug, acrylate polymer, Methocel K100M, and permeation enhancer were taken as shown in **Table 1**, water was added to the required weight, and the mixture stirred on a magnetic stirrer for 1 h. The films were prepared by a solvent evaporation method using rectangular glass moulds of size 6.7 × 4.5 cm. All the patches were wrapped in aluminum foil and stored in a desiccator until further evaluation.

Evaluation of Drug in Adhesive Patch: The formulated transdermal patches were evaluated for various physicochemical properties like thickness, drug content, percentage moisture content, percentage moisture uptake, folding endurance, tensile strength, peel adhesion and *in-vitro* drug release as reported in literature [15-19].

Factorial Design Based Formulation: On the basis of initial screening studies two drug in adhesive patches were subjected to 3^2 experimental design (Design-Expert® Software Stat-Ease, Inc) wherein two factors *i.e.*, solubilizer and permeation enhancer was varied at three levels and the response measured was *in-vitro* drug release, peel adhesion strength and tensile strength. Analysis of variance (ANOVA) and all statistical analysis was also performed using the same software.

TABLE 2: EXPERIMENTAL DOMAIN FOR NOVACRYL- PEG 400 DIAP

Factor	Independent variable	Lower level (Coded-1)	Middle Level (Coded 0)	Upper level (Coded+1)
Methocel K-100M (mg)	X_1	100	137.5	175
PEG400 (mg)	X_2	45	90	135

TABLE 3: EXPERIMENTAL DOMAIN FOR NOVACRYL-TRANSCUTOL DIAP

Factor	Independent variable	Lower level (Coded-1)	Middle Level (Coded 0)	Upper level (Coded+1)
Methocel K-15M (mg)	X_1	100	137.5	175
Transcutol (mg)	X_2	45	90	135

For Rosuvastatin calcium loaded transdermal film based on Novacryl as a film former, two designs were selected. In the first design, the effect of independent variables like Methocel K -100 M and PEG 400 were studied on the response variables **Table 2**. In the second design, the effect of independent variables like Methocel K -100 M and Transcutol was studied on the response variables **Table 3**.

Characterization of Optimized Drug in Adhesive Patch:

Differential Scanning Calorimetry of Optimized DIAP: Differential scanning calorimetry (DSC) is a useful tool for analyzing solid-state interactions of the excipients and the drug. In the case of DIAP, which are essentiality matrix systems, it gives an indication of the physical state in which the drug exists in the matrix system. The thermograms were obtained for the drug and drug in an adhesive patch. DSC analysis was performed using a DSC 6220 (SII Nanotechnology, SEIKO) differential scanning calorimeter. Accurately weighed samples were placed in aluminum pans sealed with a lid. Al_2O_3 was used as a reference. During the scanning process, a heating rate of 10 °C/ minute was applied in the temperature range from 20 °C to 150 °C.

X-ray Diffraction of Optimized DIAP: XRD studies were performed using the Bruker D8 Advance instrument. The samples were scanned over a 2θ range of 0°–90° at a rate of 0.05°/second.

Scanning Electron Microscopy of Optimized DIAP: Scanning electron microscopy produces images of a sample by scanning the surface with a focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that contain information about the surface topography. JEOL JSM 7600F Field Emission Scanning Microscope was used for studying the morphology of drug in adhesive patches. Patches were subjected to analysis; images were collected at an acceleration voltage of 5.0 KV using backscattered electron detector.

RESULTS AND DISCUSSION:

Evaluation of Rosuvastatin Calcium Loaded Drug on Adhesive Patch:

TABLE 4: EVALUATION OF ROSUVASTATIN CALCIUM LOADED DIAP

Formulation Code	Tensile Strength (Kg/cm^2)	Peel adhesion strength (N/25 mm)	% Cumulative Release
CPG	6.58 ± 0.08	5.27 ± 0.11	57.63 ± 1.11
MPG	4.63 ± 0.59	6.1 ± 0.23	58.99 ± 0.94
NPG	5.20 ± 0.04	5.14 ± 0.40	61.15 ± 1.24
CI	9.33 ± 0.56	6.52 ± 0.87	85.82 ± 0.51
MT	11.90 ± 0.79	5.60 ± 0.19	85.20 ± 1.31
NT	6.41 ± 0.85	7.38 ± 0.34	96.33 ± 1.87
CL	6.51 ± 0.42	4.40 ± 0.56	39.29 ± 0.89
ML	4.95 ± 0.12	6.74 ± 0.98	60.94 ± 1.41
NL	5.33 ± 0.06	8.10 ± 0.73	34.93 ± 0.71
CPEG400	8.46 ± 0.33	10.74 ± 0.25	62.59 ± 1.01
MPEG400	10.09 ± 0.21	12.84 ± 0.57	79.49 ± 0.85
NPEG400	6.25 ± 0.18	7.51 ± 0.92	94.81 ± 1.56

As can be seen from **Table 4**, the % cumulative release at the end of 24 h for the formulations containing Methocel K100M was found to be between 34% to 96%. The formulated films showed thickness ranging from 0.08 mm to 0.18 mm. The % drug content for all patches was in the range of 95.27% to 97.67%. The patches showed moisture content and moisture uptake in the range of 6.66% to 7.14% and 14.28% to 15.38% respectively.

Folding endurance values of the patches were greater than 250 folds. The tensile strength, peel adhesion strength values are as seen in **Table 4**. Preliminary evaluation of trial batches shows the patches have tensile strength values in the range of 4.63 to 11.90 kg/cm^2 and peel adhesion strength in the range of 4.40 to 12.84 N/25 mm. The % cumulative release of drug at the end of 24 hrs was found to be 96.33% and 94.81% for Novacryl-Transcutol (NT) and Novacryl–PEG 400 (NPEG400) patch respectively which was much higher than other combinations. Both the formulations also show moderate values of tensile strength and peel adhesion strength.

Factorial Design Based Formulation: Based on evaluation of preliminary batches of formulation Novacryl-Transcutol (NT) and Novacryl –PEG 400 (NPEG400) patches were selected for further study.

These two combinations were subjected to a 3^2 factorial design [20-23]. The experiments, as defined in **Tables 5** and **6** were performed.

TABLE 5: 3^2 FACTORIAL DESIGN FOR NOVACRYL–PEG 400 DIAP

Formulation code	X_1 X_2	% Cumulative Release	Peel adhesion strength (N/25mm)	Tensile Strength (Kg/cm^2)
$NPEG400_1$	-1 +1	71	13.68	5.87
$NPEG400_2$	-1 -1	70	17.53	6.58
$NPEG400_3$	0 0	86.2	13.55	5.75
$NPEG400_4$	0 +1	87.71	11.02	4.71
$NPEG400_5$	+1 0	92.28	13.25	5.2
$NPEG400_6$	0 -1	84.56	15.23	6.27
$NPEG400_7$	+1 -1	90.3	16.28	6.16
$NPEG400_8$	-1 0	71	13.68	5.87
$NPEG400_9$	+1 +1	96.35	10.68	4.31

Statistical analyses of the responses were performed. The values of "Prob>F" less than 0.05 indicates that the model terms are significant. Regression analysis was performed on the results, and polynomial equations were derived for the responses as a function of the independent variables. The polynomial equations can be used to draw conclusions after considering the magnitude of each coefficient and the mathematical sign it carries.

Polynomial Equation in Terms of Coded Factors:

% cumulative release = + 85.88 + 10.91*A + 1.95*B + 0.8875 *AB - 4.09*A^2 + 0.4100*B^2

Peel Adhesion Strength = +13.66 - 0.4567*A -2.60 *B

Tensile Strength = +5.54 -0.2917*A - 0.8367*B

From the polynomial equation it can be seen that for % cumulative release, A & B are significant terms. From **Table 5** and **Fig. 1** it can be seen that high levels of solubilizer and permeation enhancer increases the % cumulative release. Formulation $NPEG400_9$ gave highest percentage of drug release (96.35%), as compared to the formulation $NPEG400_2$ (70%). As the concentration of hydrophilic polymer Methocel K100M increased in the formulations, the drug release rate increased substantially.

It may be due to initial rapid dissolution of the hydrophilic polymer when the patch is in contact with the hydrated skin, resulting in the accumulation of high amounts of drug on the skin surface and thus leading to saturation of the skin with drug molecules [13]. Plasticization effect of PEG 400 may lead to less rigid and more relaxed network of the PSA. Increased flexibility of the PSA by increasing the intermolecular separation of the polymer chains may be the reason for higher release of drug from the patch.

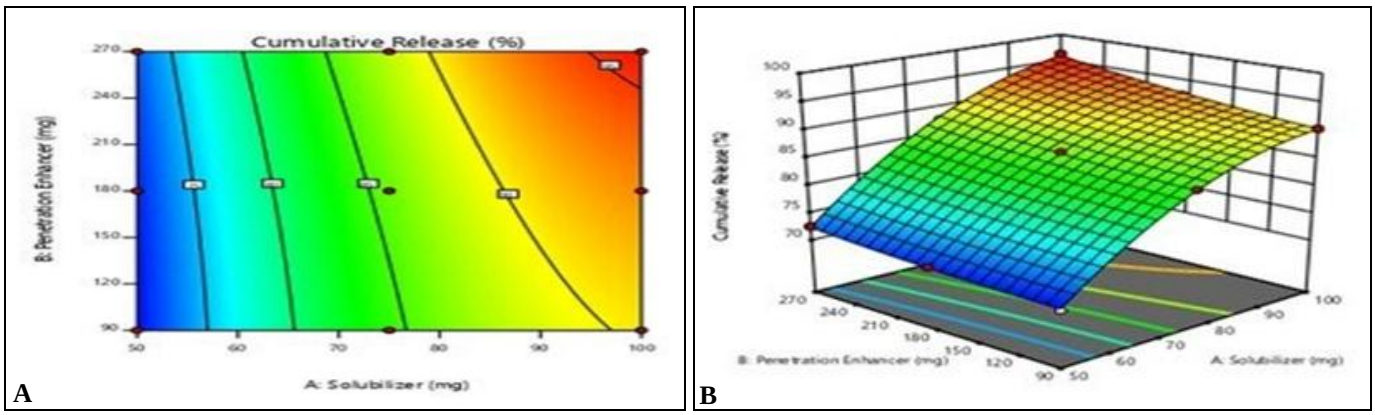

FIG. 1: CUMULATIVE % RELEASE FOR NOVACRYL –PEG 400 DIAP: (A) CONTOUR PLOT (B) 3D RESPONSE SURFACE PLOT

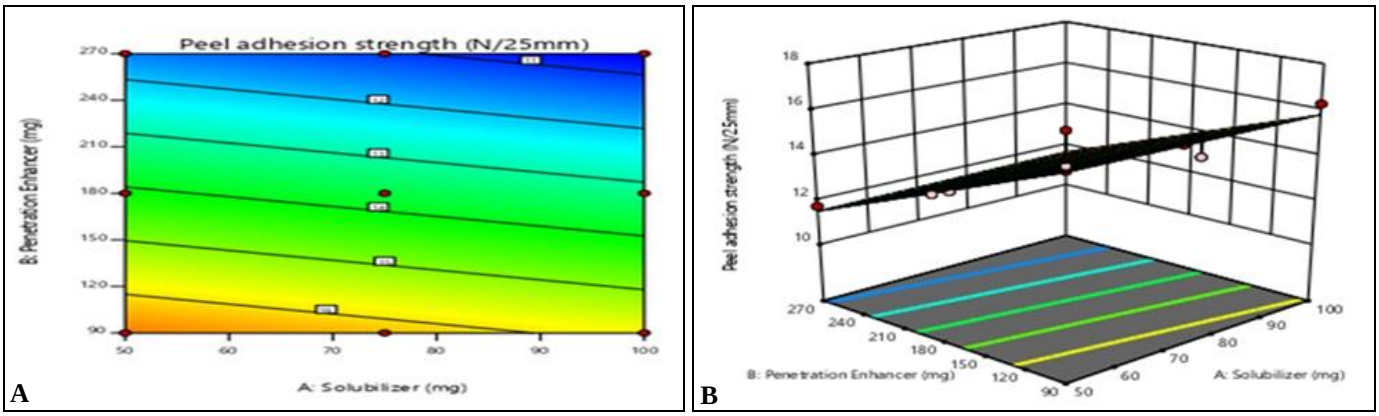

FIG. 2: PEEL ADHESION STRENGTH FOR NOVACRYL –PEG 400 DIAP: (A) CONTOUR PLOT (B) 3D RESPONSE SURFACE PLOT

However, an increase in levels of penetration enhancer shows a decrease in the values of peel adhesion in **Table 5** and **Fig. 2**. A negative sign of the coefficient for penetration enhancer indicates an

antagonistic effect of this variable peel adhesion strength. So at a low level of this variable, higher value of peel adhesion strength is seen. This may be due to PEG 400 induced plasticization of the PSA, leading to a depression of the glass transition temperature and loss of the soft, tacky properties that are necessary for a PSA [24]. The terms A and B do not show significant effect on tensile strength of patch **Table 5** and **Fig. 3**.

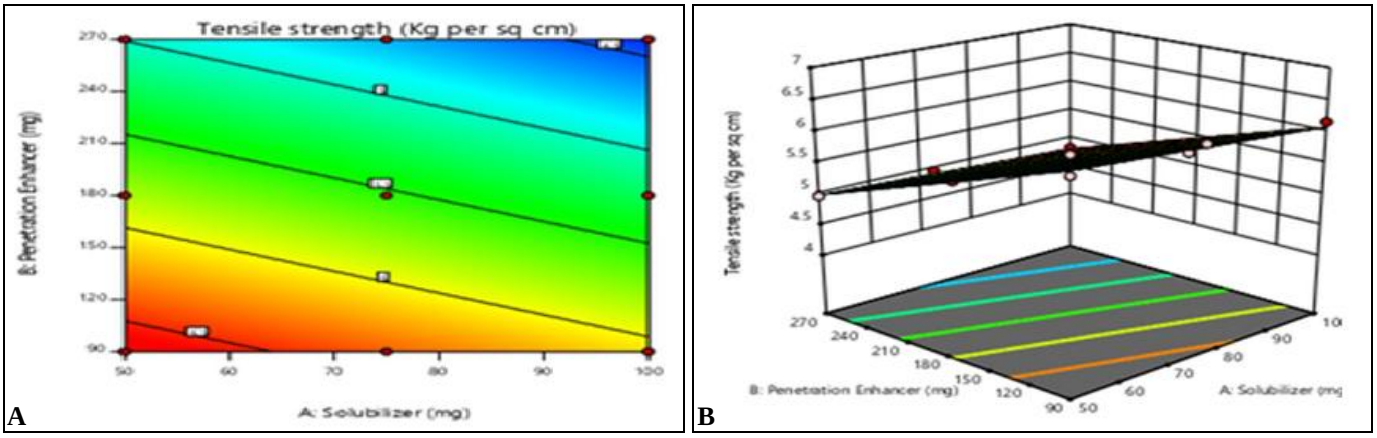

FIG. 3: TENSILE STRENGTH FOR NOVACRYL-PEG 400 DIAP: (A) CONTOUR PLOT (B) 3D RESPONSE SURFACE PLOT

TABLE 6: 3^2 FACTORIAL DESIGN FOR NOVACRYL–TRANSCUTOL DIAP

Formulation code	X_1 X_2	% Cumulative Release	Peel adhesion strength (N/25 mm)	Tensile Strength (Kg/cm^2)
NT_1	-1 +1	69.75	12.84	13.89
NT_2	-1 -1	67.67	16.47	15.41
NT_3	0 0	88.21	12.88	12.75
NT_4	0 +1	90.45	11.83	12.33
NT_5	+1 0	94.59	12.04	10.87
NT_6	0 -1	85.67	15.89	13.25
NT_7	+1 -1	93.07	14.86	10.91
NT_8	-1 0	69.35	13.59	15
NT_9	+1 +1	96.35	11	9.27

Polynomial Equation in Terms of Coded Factors:

% cumulative release = + 88.26 + 12.87*A + 1.69*B + 0.3000*AB-6.31*A^2-0.2233*B^2

Peel Adhesion Strength = +12.88-0.8333*A-1.92*B-0.0575*AB- 0.0667*A^2+0.9783*B^2

Tensile Strength = + 12.63-2.21*A-0.6800 *B

From the polynomial equation, it can be seen that for % cumulative release, A & B are significant terms. From **Table 6** and **Fig. 4**, and it can be seen that high levels of the solubilizer and permeation enhancer increases the % cumulative release. Formulation NT_9 gave highest percentage of drug release (96.35%), as compared to the formulation NT_2 (67.67%). As the concentration of hydrophilic polymer Methocel K100M increased in the formulations, the drug release rate increased substantially which is comparable to the effect seen in the case of formulation $NPEG400_9$. In case of peel adhesion strength, the term A is insignificant whereas B is significant. However a negative sign of the coefficient for penetration enhancer indicates an antagonistic effect of this variable on peel adhesion strength and increase in levels of penetration enhancer shows a decrease in the value of peel adhesion strength **Table 6** and **Fig. 5**.

This may be due to transcutol induced plasticization of the PSA, leading to a depression of the glass transition temperature and loss of the soft, tacky properties that are necessary for a PSA [25].

For the tensile strength of the patch, the term B is insignificant, and a negative sign of the coefficient for term A indicates better values of tensile strength at lower levels of solubilizer due to lesser charges in the physiochemical properties of the original PSA **Table 6** and **Fig. 6**.

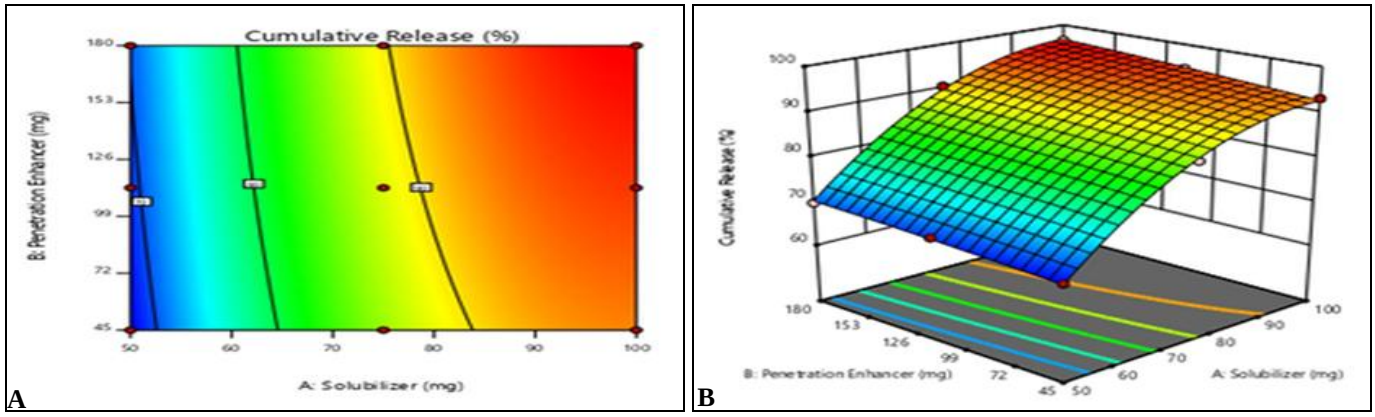

FIG. 4: CUMULATIVE % RELEASE FOR NOVACRYL –TRANSCUTOL DIAP: (A) CONTOUR PLOT (B) 3D RESPONSE SURFACE PLOT

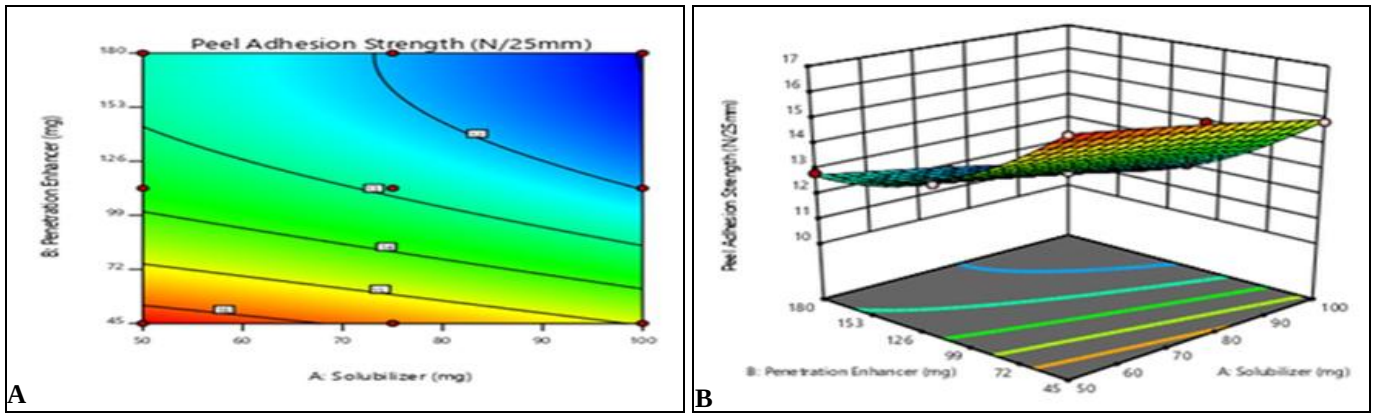

FIG. 5: PEEL ADHESION STRENGTH FOR NOVACRYL–TRANSCUTOL DIAP: (A) CONTOUR PLOT (B) 3D RESPONSE SURFACE PLOT

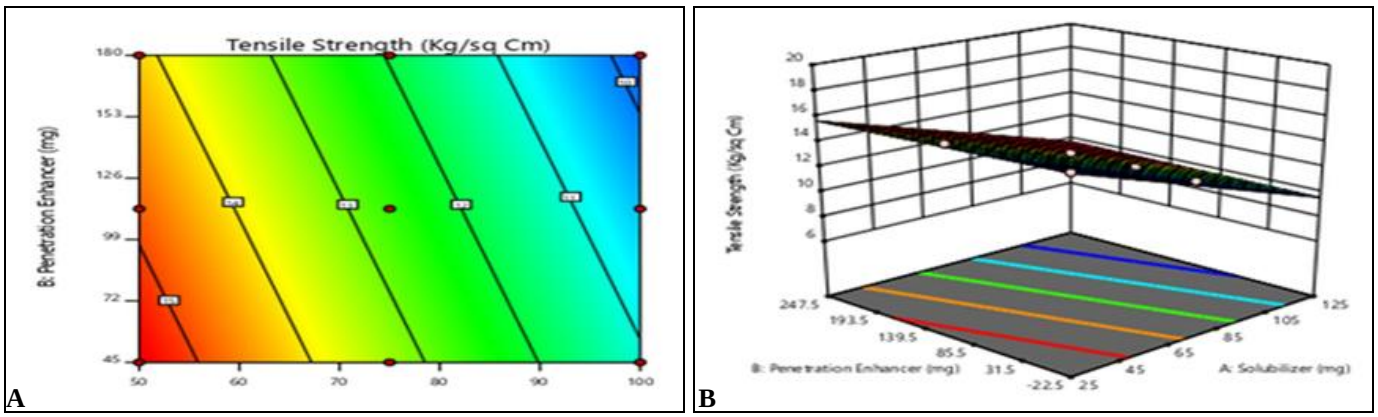

FIG. 6: TENSILE STRENGTH FOR NOVACRYL –TRANSCUTOL DIAP: (A) CONTOUR PLOT (B) 3D RESPONSE SURFACE PLOT

Numerical optimization data provided by the software gives solutions for optimized batches of the formulation. As can be seen from **Table 7**, novacryl –PEG 400 transdermal film prepared using 100 mg of the solubilizer and 90 mg of penetration enhancer gave response values that are in close agreement with the predicted values provided by the software.

TABLE 7: OBSERVED AND PREDICTED VALUES FOR OPTIMIZED NOVACRYL –PEG 400 DIAP

Optimized Patch	A: Solubilizer mg	B: Penetration Enhancer mg	Cumulative Release %	Peel adhesion Strength N/25 mm	Tensile Strength Kg /sq cm
Observed	100	90	92.10	15.21	5.11
Predicted	100	90	90.276	15.80	6.08

As can be seen from **Table 8**, novacryl-transcutol transdermal patch prepared using 100 mg of solubilizer and 45 mg of penetration enhancer gave response values that are in close agreement with the predicted values provided by the software.

TABLE 8: OBSERVED AND PREDICTED VALUES FOR OPTIMIZED NOVACRYL –TRANSCUTOL DIAP

Optimized Patch	A: Solubilizer mg	B: Penetration Enhancer mg	Cumulative Release %	Peel adhesion Strength N/25 mm	Tensile Strength Kg /sq cm
Observed	100.000	45.000	93.72	13.48	9.89
Predicted	100.000	45.000	92.60	14.942	11.103

Characterization of Optimized Drug in Adhesive Patch: As seen in **Fig. 7A**. DSC analyses for the drug Rosuvastatin calcium show a sharp endothermic peak at 152.8 °C corresponding to its melting point which is not seen in the case of its DIA patch, **Fig. 7B**. This may be due to the dispersion of the drug in the molecular form in the adhesive and also the minimal amount in which it is present in the drug in adhesive film [25-26].

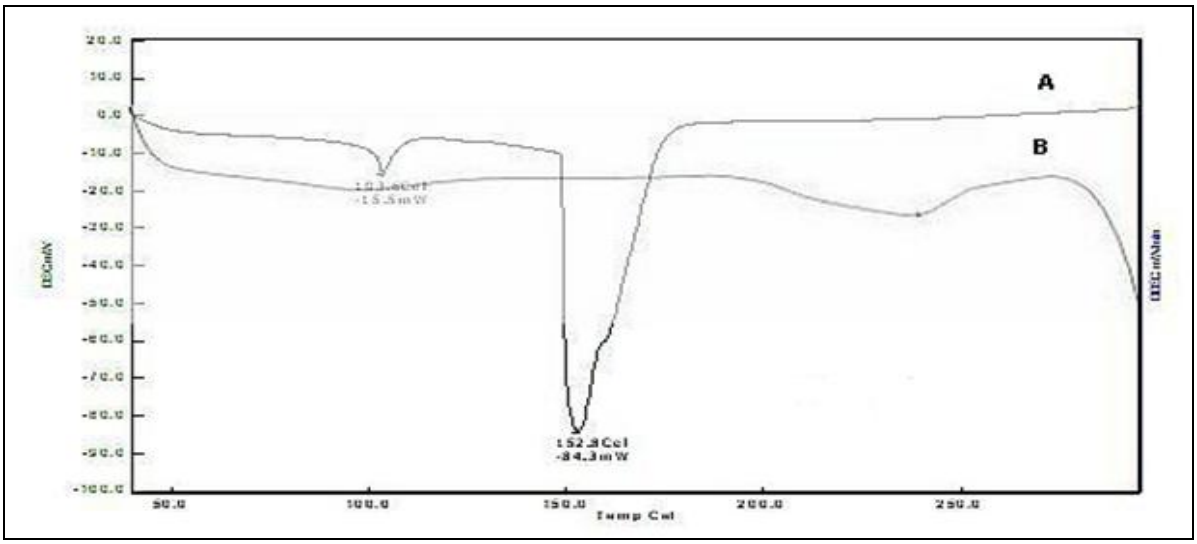

FIG. 7: DSC THERMOGRAM OF ROSUVASTATIN CALCIUM (B) ROSUVASTATIN CALCIUM DIAP

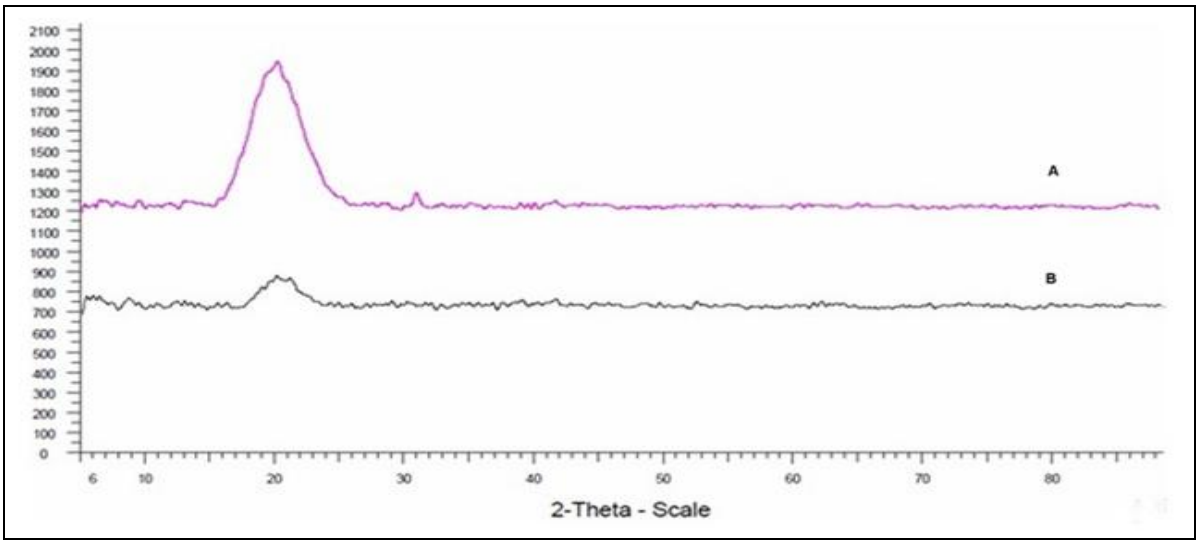

FIG. 8: X-RAY DIFFRACTION PATTERN FOR (A) ROSUVASTATIN CALCIUM (B) ROSUVASTATIN CALCIUM LOADED DIAP

In **Fig. 8A** the intense peak for Rosuvastatin calcium can be seen at 2θ of 20°, however in the case of the drug in an adhesive patch, **Fig. 8B,** the intensity of peak appearing at 2θ of 20° is seen to be significantly reduced, indicating the amorphous nature of drug [25-26].

As seen in **Fig. 9A** and **Fig. 9B** the surface morphology confirms the compatibility of the drug with the matrix polymer showing a homogeneous smooth surface. This may be due to the habit modification by Methocel 100 M due to the different extent of adsorption on different faces of the crystal, the extent of which is dependent on the hydrogen bonding functional groups that are exposed at each face of the crystal [27].

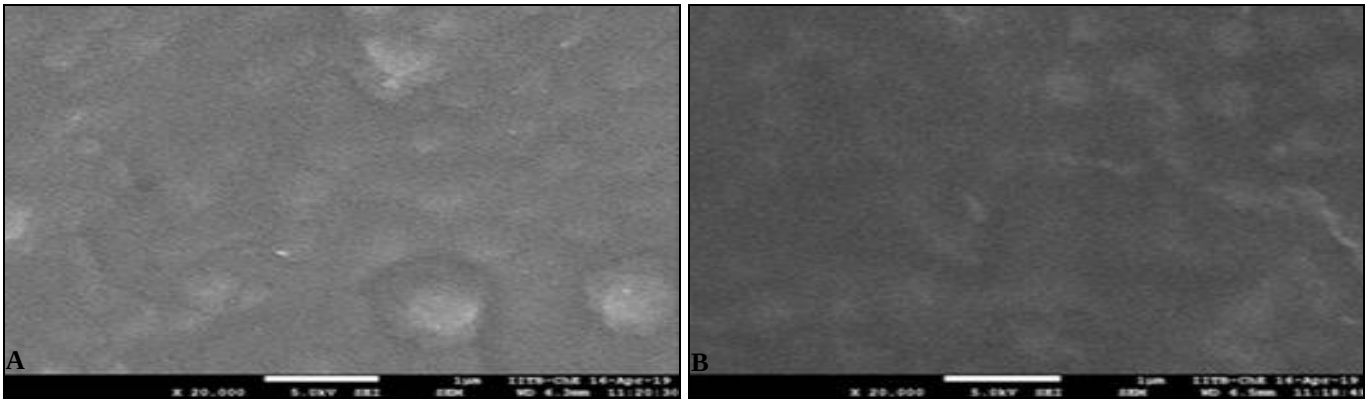

FIG. 9: SEM IMAGE FOR: (A) ROSUVASTATIN CALCIUM LOADED NOVACRYL–PEG 400 DIAF (B) ROSUVASTATIN CALCIUM LOADED NOVACRYL–TRANSCUTOL DIAP

CONCLUSION: Thus, the present study involves the formulation of a transdermal patch of Rosuvastatin calcium using a water-based pressure-sensitive hydrophobic adhesive matrix. It can be stated that acrylic emulsion PSA *i.e.* Novacryl, can provide sustained delivery of the drug as well as impart adhesive properties to the drug in the adhesive patch. The incorporation of a solubilizer and permeation enhancer modified drug release, peel adhesion strength, and tensile strength of the drug-in-adhesive film. The results indicate the need to maintain a fine balance between drug release enhancement and adhesive properties of the transdermal patch. The transdermal formulation can be considered as a potential alternative to the oral dosage form.

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CONFLICTS OF INTEREST: Nil

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