# Evaluation of Polymerized Rosin for the Formulation and Development of Transdermal Drug Delivery System: A Technical Note

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## INTRODUCTION

Rosin is a solid resinous mass obtained naturally from pine trees. Principally it contains resin acids (abietic and pimaric) and a small amount of nonacidic components. Rosin and rosin derivatives are widely used in paints, varnishes, cosmetics, printing inks, and chewing gums. Rosin and rosin derivatives have been pharmaceutically evaluated as microencapsulating materials[1,2] and as anhydrous binding agents in tablets.[3,4] Rosin and its esters are reported to have excellent film-forming properties and can be used for enteric coating and delayed release of drugs.[5,6] Being natural in origin, rosin and its derivatives are expected to be biodegradable in vivo.[7] Some rosin biopolymers are reported to have excellent biocompatibility and degradation features.[8] One of the prominent inherent properties exhibited by rosin biomaterials is their film-forming ability. In view of this property, they promise utility in the development of film-based drug delivery systems and dosage forms. It therefore seems logical to consider the possible use of rosins in the development of transdermal drug delivery systems, which has not been attempted so far as indicated in the literature.

Skin, the largest organ of the human body, provides a painless and patient-friendly interface for systemic drug administration. In addition to providing a leading edge over injections and oral routes by increasing patient compliance and avoiding first pass metabolism, respectively; the transdermal route provides sustained and controlled delivery. It also allows continuous input of drugs with short biological half-lives and can eliminate pulsed entry into systemic circulation, which often causes undesirable side effects.[9-12] Technological discoveries, over the last decade, have proven the feasibility of using several methodologies for enhancing transdermal drug delivery.[13] With a diverse set of tools to enhance skin permeability, the future of transdermal drug delivery looks brighter. The challenge now lies in converting these discoveries into useful products using newer excipients and technologies.[14]

In spite of their excellent film-forming property, rosins have been scantly evaluated for transdermal drug delivery probably owing to concerns regarding their dermal toxicity. However, the dermal response of rosin has been custom altered by specific chemical modifications to suit the needs of the cosmetics and chewing gum industries, where they find wide applications.[15] In view of these wide-ranging applications, we aim to investigate polymerized rosin (PR) for its use in transdermal drug delivery systems. PR exhibits excellent film-forming property with sustained release applications.[16] PR is light yellow in color with acid value 151 (mg of KOH), softening point 75°C to 80°C, molecular weight (Mw) = 680, polydispersity Mw/Mn = 1.01, and glass transition temperature (Tg) = 65°C. PR is prepared by polymerization of abietic acid present in gum rosin, which is changed to a dimer, by linking 2 of its molecules.[17,18] This reaction gives the polymerized gum rosin. Compared with ordinary gum rosin it has a series of excellent properties such as good film-forming ability, higher softening point, noncrystalline nature, good oxidation-resistance, and higher viscosity in organic solvent. The structure of di-abietic acid is shown in Figure 1.

Diltiazem hydrochloride (DTH) is a calcium channel blocker used in the treatment of arrhythmia, angina pectoris, and hypertension. The literature reveals that DTH undergoes variable and extensive first pass metabolism before entering into systemic circulation.[19] Although the liver is considered to be the major organ of DTH biotransformation, the extrahepatic organs, such as intestine and lungs, contribute to the first pass uptake and systemic elimination of DTH. Transdermal administration of drugs that undergo first pass metabolism can improve the bioavailability and reduce the dosing frequency compared with the oral route. DTH has been already investigated for transdermal delivery.[20,21] In the present study, PR patches were prepared with polyvinyl pyrrolidone (PVP) using DTH as drug model. These patches were evaluated for moisture content, water absorption, mechanical properties, in vitro drug release and in vitro skin permeation studies.

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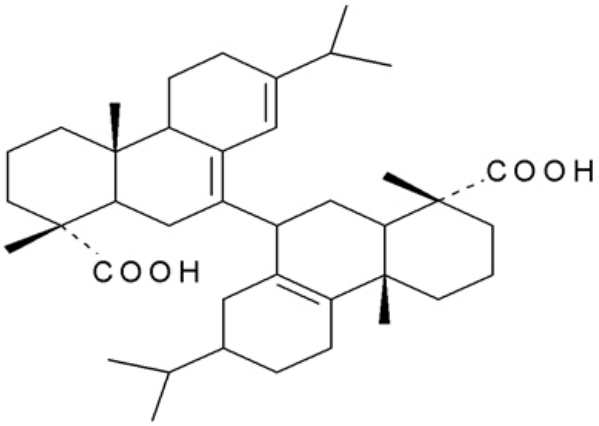


**Figure 1.** Structure of di-abietic acid.

## MATERIALS AND METHODS

### *Materials*

PR was received as gift sample from Derives Resiniques and Terpeniques Inc, Gambetta, France. PVP (K value: 26-35) (Himedia Laboratories Pvt, Ltd, New Delhi, India), Polyvinyl alcohol (S.D. Fine Chemicals Ltd, India), Dibutyl phthalate (Ranbaxy Laboratories Ltd, Gurgaon, India), Potassium chloride (S.D. Fine Chemicals Ltd, India), and Chloroform (Qualigens Laboratories, Mumbai, India). DTH was obtained from Dr. Reddy's Laboratories, Hyderabad, India, and used as received.

### *Methods*

*Preparation of Films*

Matrix type transdermal patches composed of different ratios of PR, PVP, and DTH (Table 1) were prepared by solvent evaporation technique in a glass ring. The bottom of the ring was wrapped with aluminum foil on which backing membrane was cast by pouring 3% wt/vol PVA solution followed by drying at 60°C for 8 hours. Drug matrix was prepared by dissolving requisite amount of drug, PR, and PVP in chloroform. To this solution dibutyl phthalate (30% wt/wt of polymer composition) was added and stirred. The uniform dispersion obtained was cast on PVA backing membrane and dried at 60°C for 8 hours. Controlled solvent evaporation was achieved by placing an inverted funnel over the Petri dish. The dry films were removed and kept in a dessicator until used.

*Physicochemical Properties of the Films*

The films were evaluated for the following physicochemical properties:

*Thickness*: The thickness of the patch was determined using micrometer screw gauge (Mitoyoto, Tokyo, Japan), recording mean of 6 determinations.

*Drug content uniformity:* Films of specified area were cut and weighed accurately. Pieces were taken into a 100-mL volumetric flask and 60-mL phosphate buffer solution (pH 7.4) was added and kept in a shaker for 12 hours. A blank was performed using a drug-free film. The solution was filtered and samples were analyzed spectrophotometrically for DTH content at 236 nm.

*Moisture content:* The prepared patches were cut into 20 × 50 mm strips. The strips were then weighed individually and kept in a dessicator containing activated silica[19] at 30°C for 12 hours. The films were reweighed individually until a constant weight was obtained. Percentage of moisture content was then calculated based on the change in the weight with respect to the initial weight of the film.

*Water absorption studies:* The water absorption capacities of various films were determined at 75% and 93% relative humidity (RH). Films were cut into 25 × 60 mm strips. A strip was weighed and kept in a dessicator at 40°C for 24 hours, removed, and exposed to RH conditions of 75% (containing saturated solution of sodium chloride) and 93% (containing saturated solution of ammonium hydrogen phosphate) in different desiccators at room temperature. Weight was taken periodically until a constant weight was obtained. The water absorption capacity of the films (in weight %) was calculated in terms of percentage increase in the weight of film over the initial weight of the specimen.[22]

*Drug carrier interaction:* Thin layer chromatography (TLC) method was used for the drug carrier interaction studies.[23]

*Mechanical properties:* The mechanical properties were determined using plastic tensile test performed using an Instron Instrument (model 4467, Instron Corp, Canton, MA) based on standard ASTM test method. The measurements were made at a gauge length 50 mm with cross head speed (CHS) of 10 mm/min. The test was performed at 50% RH at 25°C. Tensile strength and percentage elongation were computed with at least 6 repetitions.

**Table 1.** Composition of Prepared Patches*

| Formulations | Ratio of PR/PVP | DTH (% wt/wt of polymer) |
|---|---|---|
| F1 | 6:4 | 10 |
| F2 | 7:3 | 10 |
| F3 | 8:2 | 10 |
| F4 | 6:4 | 15 |
| F5 | 7:3 | 15 |
| F6 | 8:2 | 15 |

*PR indicates polymerized rosin; PVP, polyvinyl pyrrolidone; and DTH, diltiazem hydrochloride. All formulations contain 30% wt/wt dibutyl pthalate.

*In Vitro Drug Release Studies*

The paddle over disc method was employed for assessment of the release of the drug from the prepared patches.[24] Dry films of known thickness were cut into circular shape, weighed, and fixed over a glass plate with an adhesive. The plate was then placed in a 500-mL phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32°C ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) were withdrawn at appropriate time intervals up to 16 hours and analyzed for drug content at 236 nm using Shimadzu double beam UV-visible spectrophotometer (Shimadzu, Kyoto, Japan). The experiment was performed in triplicate and the mean value was calculated.

*In Vitro Permeation Studies*

Modified Franz diffusion cell was used for these studies. Full thickness abdominal skin of male Wistar rats weighing 140 to 200 g was used. Hair from the abdominal region was carefully removed and an excision in the skin was made. The dermal side of the skin was thoroughly cleaned of any adhering tissues or blood vessels and equilibrated for an hour in pH 7.4 buffer before running the experiment. The skin piece was mounted between the compartments of the diffusion cell with the epidermis facing upward into the donor compartment. The patch to be tested was placed on the skin. Phosphate buffer solution (24 mL) containing 20% vol/vol polyethylene glycol (PEG) 400 (37°C ± 1°C) was used as receptor phase and agitated with a magnetic stirrer. The top of the cell was covered with aluminum foil to avoid drug photosensitivity. Samples (3 mL every time) were withdrawn at regular periods through the sampling port, and fresh receptor fluid solution was added. Absorbance of sample was measured spectrophotometrically at 236 nm against blank (20% vol/vol PEG 400 solution).[25,26] The cumulative amount of drug permeated was plotted against time.

*Skin Irritation Studies*

Skin irritation studies were performed on healthy rabbits (average weight: 1.5 to 2.25 kg). The dorsal surface (50 $cm^2$) of the rabbits was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. Representative patches (F3 and F6) were placed over the skin with the use of adhesive tape and were removed after 24 hours. The resulting reaction was evaluated using weight score. The average of 24 and 72 hours reading represent the final scores according to the method of Draize et al.[27]

## RESULTS AND DISCUSSION

### *Evaluation of Transdermal Patches*

Table 1 shows the composition of PR patches containing varying proportion of PVP and DTH.

Further, as shown in Table 2, the drug content analysis of the prepared formulations showed that the process used to prepare the patches in this investigation is capable of giving uniform drug content and minimum batch variability. The percentage moisture content of the patches was calculated from the weight difference relative to final weight. The moisture content in the formulation was found to increase with the increasing concentration of drug and hydrophilic polymer PVP. The water absorption capacity was found to increase with increasing concentration of hydrophilic polymer PVP and with increasing RH. However, the water absorption capacity was found to be as low as 1.130% ± 0.73% with F6 at 75% in all formulations at both the humidity conditions. The low absorption capacity is likely to protect the formulation from microbial contamination and bulkiness of the patches.[28]

*Drug carrier interaction*: TLC studies were performed to investigate any chemical interaction between drug and the excipients. The results obtained show that the $R_f$ values of drug and drug-excipient solutions did not show any significant difference suggesting that there was no interaction between the drug and excipients (Table 2).

**Table 2.** Drug Content Uniformity, $R_f$ Values, Moisture Content, and Water Absorption Capacity (in wt %) of Various Formulations*

| Formulation | Amount of Drug per 100 mg of Film (mg) | $R_f$ Values | | % Moisture Content | Water Absorption (wt %) | |
|---|---|---|---|---|---|---|
| | | Drug | D:E Solution | | RH 75% | RH 93% |
| F1 | 6.97 ± 0.17 | 0.74 | 0.75 | 1.603 ± 0.13 | 5.913 ± 0.78 | 8.707 ± 0.15 |
| F2 | 7.45 ± 0.75 | 0.74 | 0.75 | 1.313 ± 0.62 | 3.206 ± 0.37 | 5.413 ± 0.75 |
| F3 | 7.20 ± 0.32 | 0.75 | 0.76 | 0.690 ± 0.59 | 1.210 ± 0.96 | 2.915 ± 0.85 |
| F4 | 10.32 ± 0.40 | 0.76 | 0.76 | 1.776 ± 0.69 | 6.12 ± 0.52 | 8.51 ± 0.69 |
| F5 | 9.98 ± 0.12 | 0.74 | 0.74 | 1.450 ± 0.27 | 3.013 ± 0.81 | 5.513 ± 0.27 |
| F6 | 10.17 ± 0.53 | 0.75 | 0.76 | 0.821 ± 0.94 | 1.130 ± 0.73 | 2.729 ± 0.51 |

*Data represent mean ± SD of 6 determinations. RH indicates relative humidity; and D:E = drug:excipient.

The thickness of the patches (with varying ratios of PR, PVP, and drug) varied from 79 to 98 μm. The low values for standard deviation indicate physical uniformity of the patches (Table 3).

*Mechanical properties:* Mechanical properties of the patches of various formulations are shown in Table 3. The results reveal that the patches have reasonable tensile strength and moderate percentage elongation. The tensile strength increased whereas percentage elongation decreased with increasing concentration of PVP. The tensile strength results obtained in formulations indicate the risk of film cracking. But, no sign of cracking in patches was observed, which might be attributed to addition of plasticizer dibutyl phthalate (DBP) (30% wt/wt of polymer weight). Addition of DBP resulted in formation of smooth films.

### *In Vitro Drug Release Studies*

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance.[29] For in vitro release studies we employed a paddle over disk method. The results indicate that the release of drug from the patches increases with increasing concentration of PVP (Figure 2). Initial burst release was observed in patches with PR:PVP ratio 6:4 (ie, F1 and F4). This may be because of the higher percentage of PVP in these 2 formulations. PVP might need a very small time lag to establish a concentration profile in the patches resulting in a burst effect in the release studies.

F2 and F5 patches showed moderate burst effect pattern, whereas the patches of F3 and F6 showed sustained release of the drug. Maximum percentage of drug release (ie, 94%) was observed with formulation F4 and the minimum (ie, 78%) was found with formulation F3. Release studies also revealed that increase in drug loading does not show any statistically significant effect on drug release from the patch, while increase in concentration of PR in formulations decreases the release rate. It is well acknowledged that the addition of hydrophilic component to an insoluble film former tends to enhance its release rate constants.[30] This phenomenon may be due to dissolution of the aqueous soluble fraction of the film, which leads to formation of pores and decrease of mean diffusion path length of the drug molecule to be released into dissolution medium. PVP also acts as an antinucleating agent[31] that retards the crystallization of the drug and plays a significant role in improving the solubility of the drug in the polymer matrix.

**Table 3.** Mechanical Properties of Various Formulations*

| Formulation | Thickness (μm) | Tensile Strength ($N/mm^{2)}$ | Percentage Elongation |
|---|---|---|---|
| F1 | 86 ± 0/79 | 0.393 ± 0.06 | 16.5 ± 0.89 |
| F2 | 79 ± 0.27 | 0.360 ± 0.06 | 21.37 ± 0.46 |
| F3 | 89 ± 0.57 | 0.317 ± 0.09 | 29.59 ± 1.03 |
| F4 | 98 ± 0.62 | 0.370 ± 0.07 | 12.37 ± 0.35 |
| F5 | 81 ± 0.93 | 0.347 ± 0.10 | 22.13 ± 1.21 |
| F6 | 90 ± 0.21 | 0.296 ± 0.06 | 26.93 ± 0.93 |

*Data represent mean ± SD of 6 determinations.

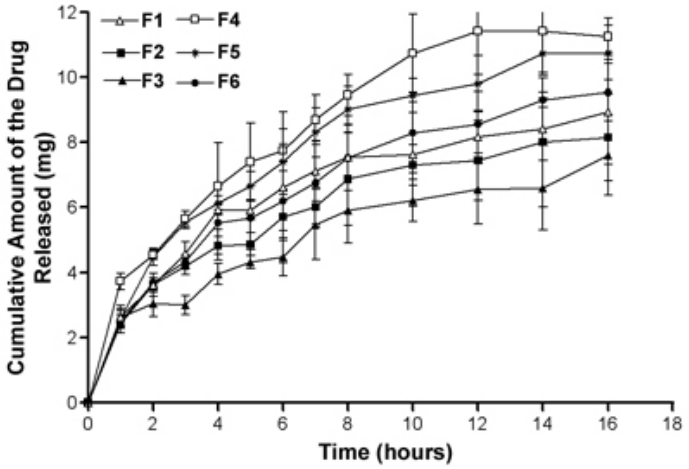


**Figure 2.** In vitro release profile of DTH transdermal film formulations. Mean ± SD of 3 independent experiments.

### *In Vitro Skin Permeation Studies*

Release of drug from transdermal patches is controlled by the chemical properties of drug and delivery form as well as the physiological and physicochemical properties of the biological membrane.[32] The in vitro permeation studies are predictive of in vivo performance of a drug.[33] Matrix or monolithic transdermal drug delivery devices are used when the rate of drug permeation through the stratum corneum is the rate-limiting step for the drug absorption. The drug release from matrix system is rapid initially and falls as the matrix is depleted of drug. Rate controlling factors include, for example, drug concentration in matrix, chemical nature of matrix material, and device geometry. Figure 3 shows the cumulative amount of DTH permeated through the rat abdominal skin, into a receptor solution, as a function of time from the various patches. The mean of cumulative amount of drug permeated per $cm^2$ of the film after 24 hours from the formulations F1 to F6 was found to be 15.32, 14.04, 10.91, 26.23, 22.39, and 15.21 μg respectively. The permeation profiles showed that the cumulative amount of drug permeated declined after 6 to 8 hours.

The permeation of drug across skin from the formulations F3 and F6 was slow but fairly constant. Formulations F1 and F4 showed rapid permeation of drug as compared with F3 and F6. Formulation F4 showed the highest permeation rate among the formulations studied. It is interesting to note

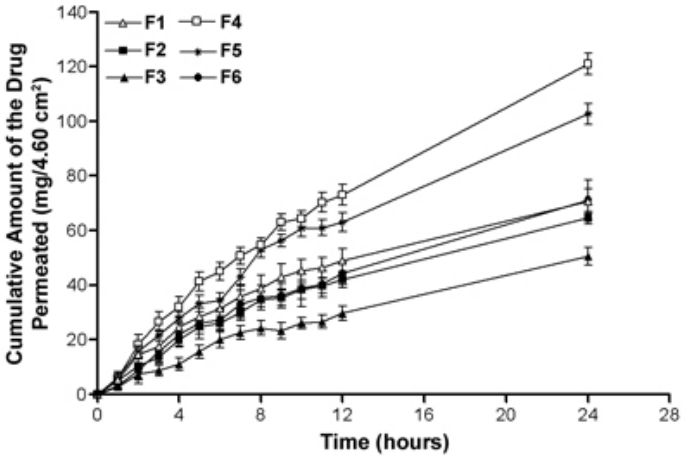


**Figure 3.** In vitro skin permeation profile of DTH transdermal film formulations. Mean ± SD of 3 independent experiments.

that formulations F1 and F4 showed burst release of the drug but the profiles behaved differently during the drug permeation study, which may be due to skin permeation of DTH and slow exposure of PVP to receptor medium. The cumulative amount of drug permeated per square centimeter of patches through the skin into the in vitro fluid plotted against time, showed almost rectilinear curve of the data. This may depict the zero order drug release kinetics of the formulations. It is evident from these studies that skin permeation of the drug increased with increase of PVP content and drug concentration in the formulation. The in vitro skin permeation experiments are known for their value for studying the rate and mechanism of percutaneous absorption of drugs.[34]

The implication of skin permeation of drug on release rate profiles of the experimental formulations should not be ignored because the skin is known to have a substantial role in variation of release kinetics.[35] At an early stage and in a steady-state of skin permeation, diffusion of drug through appendages is considered to be significant. Again selection of receptor fluid is also important for in vitro studies. A biphasic characteristic of the study fluid is desirable as the diffusion for the drug molecules through skin is routed through both aqueous and nonaqueous heterogeneous media. PEG 400 and water or normal saline are commonly selected to provide biphasic characteristics of the liquid.[36]

The enhancement of skin flux with increase of drug concentrations may be due to accumulation of a greater amount of drug on the skin surface. The improvement in skin flux with the increase of PVP content may be owing to its antinucleating effect that converts the crystalline drug into an amorphous state, which generally possesses a high-energy state with high solubility. The enhancement in drug solubility provides increased thermodynamic activity, which facilitates the skin permeation of drug.[37] The other possible mechanism of the increased permeation with increasing PVP content in film is its co-enhancing property in aqueous vehicle systems.

### *Skin Irritation Studies*

The results of skin irritation studies showed negligible erythema with prepared films when compared with control. The absence of edema indicates that the polymeric patches are compatible with the skin and hence can be used for transdermal application.

## CONCLUSIONS

Results from the present study conclude that PR in combination with PVP and with incorporation of dibutyl phthalate (30% wt/wt) produces smooth flexible films with improved tensile strength and percentage elongation. The release rate of drug from films and permeation across skin increases with increase in drug and PVP loading but is independent of film thickness. Patches containing PR:PVP (7:3) show promise for pharmacokinetic and pharmacodynamic performance evaluation in a suitable animal model. In view of the overall results reported in the present study, it may be proposed that PR can be used in the design of a matrix type transdermal drug delivery system to prolong the drug release.

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