Formulation and evaluation of oral sustained release of Diltiazem Hydrochloride using rosin as matrix forming material

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ABSTRACT
Rosin, a natural resin, was used as a hydrophobic matrix material for the controlled release, using diltiazem HCl as model drug. Matrix tablets were prepared by direct compression method using rosin as matrix forming material in different proportions and with different diluent combinations. The tablets prepared were flat faced, retained their shape throughout. The method of preparation of matrix system and its concentration were found to have pronounced effect on the release of diltiazem HCl. The release was found to follow both the first order kinetics and fickian diffusion. The drug delivery was analyzed using the paddle method according to USP XXIII. All the studies were done in phosphate buffer pH 7.4. The matrix tablets were evaluated for its thickness, hardness, friability, weight variation, drug content and invitro release studies. The results suggest that the rosin is useful in developing sustained release matrix tablets, prolong release of water soluble drug for up to 24h. Rosin thus promises considerable utility in the development of oral sustained release drug delivery systems.


INTRODUCTION
Oral sustained release systems continue to dominate the market despite the advancements made in other drug delivery systems in order to increase the clinical efficacy and patient compliance. From a practical pharmaceutical viewpoint, numerous types of polymers are currently employed to control the drug release from the pharmaceutical dosage form. Oral sustained release systems are mainly grouped into three types, e.g. reservoir, monolithic and matrix types\(^1\). Among these hydrophilic matrix tablets are preferred in the formulations since most display good compression characteristics, even when directly compressed and have adequate swelling properties that lead to a rapid formation of external layer, allowing drug release modification.

Various natural gums and mucilages have been examined as polymers for sustained drug release, in the last few decades\(^3\). The physical and structural properties and the drug release mechanisms and kinetics of these sustained release preparations determine the in vivo performance of these dosage forms. Rosin and rosin-based polymers have drug delivery applications achieving sustained/controlled release profiles.

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The use of natural polymers and their semi-synthetic derivatives in drug delivery continues to be an area of active research despite the advent of synthetic polymers. Natural polymers remain attractive primarily because they are inexpensive, readily available, capable of multitude of chemical modifications and potentially degradable and compatible due to their origin. One such biopolymer is rosin. Rosin and its derivatives have been pharmaceutically evaluated as microencapsulating materials\textsuperscript{5-7}, as anhydrous binding agents in tablets\textsuperscript{8,9}, as film coating materials\textsuperscript{10,11} as transdermal drug delivery\textsuperscript{12}. They are also used in chewing gum bases and cosmetics. Rosin, a natural product, is used as a matrix forming polymer in the present work. Rosin, is a solid resin obtained from Pinus palustris Miller and from other species of Pinus pinnae. It is composed of approximately 90% rosin acids. The rosin acids are monocarboxylic and have a typical molecular formula \(C_{20}H_{30}O_2\). The prominent ones include abietic acid with conjugated double bonds and pimaric acid with non-conjugated double bonds. The rosin acid molecules possess two chemically reactive centers, the double bonds and the carboxyl group. Being of natural origin, rosin and its derivatives are expected to be biodegradable and biocompatible\textsuperscript{13,14}. They are also widely used for their film forming properties in paints, varnishes, as a stiffening agent, and as adhesive (used in plasters, cerates, ointments and water proofing etc.).

Diltiazem is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given as oral dosage form in the treatment of angina pectoris and the management of hypertension. Its short biological half life (3-5 h), high aqueous solubility, and frequent administration (usually three to four times a day) make it a potential candidate for sustained release preparations\textsuperscript{15,16}.

**MATERIALS AND METHODS**

**Materials**

Rosin was purchased from Yucca Enterprises, Dombiuli, Thane, Diltiazem HCl was obtained as gift sample from Torrent Pharmaceuticals Ltd, Gujarat, India. Other chemicals lactose, talc, magnesium stearate, microcrystalline cellulose, dicalcium phosphate and mannitol (S.D. Fine Chemicals, Mumbai, India) were obtained commercially and used as such.

**Method**

*Diltiazem hydrochloride calibration curve*

Calibration curve of Diltiazem HCl was prepared using buffer pH 7.4 in the concentration range of 1 – 15 µg/ml. The drug was analyzed spectrophotometrically (UV 1601 Shimadzu, Japan) at 237 nm (regression coefficient \(r^2 = 0.9994\) in buffer pH 7.4)

**Formulation and preparation of matrix tablets**

Drug (Diltiazem Hydrochloride), polymer, lactose, magnesium stearate and talc were passed through sieve no. 80 separately. Six different formulations with various polymer ratios were prepared i.e. 1:1.25, 1:1.5, 1:1.75, 1:2, 1:2.75 and 1:3 by keeping the amount of lactose at 30 mg and Diltiazem at 90 mg constant with magnesium stearate 2% w/w and Talc 3%w/w, the composition is shown in Table 1.
Drug-excipient interaction studies

Preformulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy studies (Joshi et al.,) and HPTLC were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, diluents and lubricants used in case tablet formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. The earlier investigations recommended that the ratio of drug to excipients used in study was 1:5 for diluents, 3:1 for binders or disintegrants, 5:1 for lubricants and 10:1 for colorants etc, but it is observed that 1:1 ratio of drug excipients maximizes the possibility of interaction and helps in easier detection of incompatibilities. Therefore, in the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies.

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies was carried out using DSC 60, having TA60 software, Shimadzu, Japan. The instrument is very versatile as far interaction and compatibility studies at pre-formulation stage was concerned and used to evaluate melting point, enthalpy changes and glass transition temperatures of drug with excipients and polymers. Diltiazem Hydrochloride was mixed with the excipients and the DSC analysis of each sample under the analogous conditions of temperature range 40 – 300º C, heating rate 10ºC/min, nitrogen atmosphere (20ml/min) and alumina as reference. Differential Scanning Calorimetry (DSC) was performed on pure drug, excipients and composition of final formulation. DSC measurements were done on a Shimadzu DSC-60 and samples were heated at the rate of 10ºC min-1. The samples were heated in an aluminum cup up to 300ºC.

Fourier transform infrared (FTIR)

FTIR studies are very helpful in the evaluation of drug–polymer interaction studies. If there is any incompatibility between the drugs and excipients, these can be predicted by changes in the functional peaks (characteristic wave numbers). Diffuse reflectance technique was used (400 to 4000

Table 1.- Composition of Diltiazem hydrochloride matrix tablet.

<table>
<thead>
<tr>
<th>Components (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem hydrochloride</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Rosin</td>
<td>112.5</td>
<td>135</td>
<td>157.5</td>
<td>180</td>
<td>247.5</td>
<td>270</td>
</tr>
<tr>
<td>Lactose</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Talc</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Tablet compression

The matrix tablets of the above formulations were compressed in a single punch tablet compression machine. A weighted amount of the powder was introduced in the die and the die capacity was adjusted as required. Compression force was adjusted to obtain the required hardness. A batch of 25 tablets was prepared for all formulations.
cm-1), drug and various polymers were thoroughly mixed with 300mg of potassium bromide, compressed and the spectrum was obtained by placing the thin pellet in light path.

**HPTLC technique**

TLC technique is a non thermal technique very helpful in the evaluation of drug polymer interaction studies. If there is any interaction between the drug and excipients, there can be determined by change in the $R_f$ value. High performance thin layer chromatography (HPTLC) chromatogram data’s were taken on a CAMAG instrument to find out the incompatibility of the drug with excipients used in the formulation. HPTLC chromatogram of the drug and composition of final formulation were obtained by using the composition of acetic acid : water : methylene chloride : ethanol (1 : 3 : 10 : 12, v/v) as mobile phase on precoated silica gel F$_{254}$ plates used as stationary phase.

**Evaluation of tablet formulations**

**Evaluation of characteristics of powder blend and tablets**

The various characteristics of powder blend like bulk density, tapped density, angle of repose, particle size and drug content were studied. The formulated tablets were evaluated for hardness, friability, uniformity of weight and drug content.

**Drug content of formulated tablets**

Five tablets from each formulation were randomly chosen, pulverized and weight equivalent to 50mg of Diltiazem Hydrochloride was extracted with 100ml phosphate buffer (pH 7.4). Aliquot from subsequent filtered solution was further diluted in phosphate buffer (pH 7.4) in such a way that theoretical concentration was same as that of standard concentration. Resultant solutions were analyzed by using a UV spectrophotometer (in triplicate) and the average results taken.

**In vitro dissolution studies**

The dissolution studies were performed in triplicate for all the batches in a USP XXIII dissolution rate test apparatus (type II). The release studies were performed at 75 rpm in 900 ml of phosphate buffer pH 7.4 at 37 ± 0.2°C. Five milliliters aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed dissolution medium. The absorbance of the withdrawn samples was measured spectrophotometrically at 237 nm.

**Data analysis**

Different release kinetics is assumed to reflect different release kinetics mechanism. Therefore three kinetics models including zero order release equation (Eq.1), first order equation (Eq. 2) and Higuchi (Eq .3) were applied to process in vitro data to find the equation with the best fit.

$$Q = K_1t \quad \text{(Eq.1)}$$

$$Q = 100 \ (1-e^{-K_2t}) \quad \text{(Eq. 2)}$$

$$Q = K_3 \ (t)^{0.5} \quad \text{(Eq. 3)}$$

Where Q is the release percentage at time t. K1, K2 and K3 are the rate constant of zero order, first order and Higuchi model respectively.

**RESULTS AND DISCUSSION**

In the present study an attempt has been made to formulate matrix tablets of Diltiazem HCl using rosin as hydrophobic matrix material.
Drug excipient compatibility studies were carried out to check whether any compatibility related problems are associated between drug and excipients used in the formulations. DSC results revealed that the physical mixture of Diltiazem with excipients showed superimposition of the thermograms. There is no considerable change observed in melting endotherm. The DSC thermograms are shown in Figure 1. Diltiazem Hydrochloride contains two carbonyl groups, shows the values around 1679 and 1745 cm\(^{-1}\). Infrared studies reveal that both characteristic bands around 1679 and 1745 cm\(^{-1}\) were present in all spectra. While no new bands or shift in characteristic peaks appeared. IR spectra are shown in Figure 2. In HPTLC technique, \(R_f\) value for the drug was around 0.74. HPTLC studies revealed that the \(R_f\) values obtained for the drug and excipient mixture were around 0.74. HPTLC chromatograms are shown in Figure 3, 4 and 5. DSC, FTIR and HPTLC results revealed that there is no interaction between the drug and the excipients used in the formulation.

**Figure 1.** DSC thermograms.

![DSC thermograms](image)

1. DSC thermogram of diltiazem hydrochloride
2. DSC thermogram of diltiazem hydrochloride: lactose (1:1)
3. DSC thermogram of diltiazem hydrochloride: magnesium stearate (1:1)
4. DSC thermogram of diltiazem hydrochloride: talc (1:1)
5. DSC thermogram of diltiazem hydrochloride: rosin (1:1)

The pre compression parameters like bulk density and compressibility index reveal that the powder mixture had good flow properties, the results are shown in Table 2. Post compression parameters for all formulations are shown in Table 3. All the tablets were found to pass the uniformity of weight. Content of Diltiazem HCl from all formulations was found in the range of 98.5 to 101.0%.

The hardness of tablets from all formulations was between 4 and 5 kg/cm\(^2\). All the formulations showed friability between 0.55 and 0.85% indicating that the tablets could withstand the mechanical shock. The performance of sustained release formulation has been reported to be greatly affected by physicochemical properties of polymer. Six different combination of polymer: drug was used to

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prepare the sustained release matrix tablets. It was observed that the amount of polymer influences the drug release. In vitro release study results revealed that the release of drug was retarded with the proportional increase of the polymer concentration. Release results are shown in Figure 6. 98.0% release was observed in 12 h for the ratio of 1:1.25, in 16 h for 1:1.5 and in 24 h for 1:1.75 (Drug: Polymer). 1:1.75 (drug: polymer) ratio showed 98.0% release in 24 h, which was comparable to market formulation of Diltiazem Hydrochloride. Release results are shown in Figure 7. Beyond this ratio 1:1.75, release of drug was retarded this may be due to the hydrophobic nature of the polymer, which prevents the penetration of the dissolution medium into the matrix tablets leading to slower dissolution and diffusion of the drug molecules from the matrix system.

**Figure 2.** IR spectra of drug and physical mixtures.

![IR spectra](image)

**Table 2.** Pre-compression parameters for diltiazem hydrochloride powder blend.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk Density (g/cc)</td>
<td>0.62±0.15</td>
</tr>
<tr>
<td>Tapped density (g/cc)</td>
<td>0.76±0.18</td>
</tr>
<tr>
<td>Bulkiness (cc/g)</td>
<td>1.61±0.25</td>
</tr>
<tr>
<td>Carr’s index</td>
<td>18.42±2.5</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>21.0±3.5</td>
</tr>
</tbody>
</table>
The optimized formulation was then subjected to check the effect of release enhancers like lactose, MCC, DCP and Mannitol. The composition is shown in Table 4, and it was subjected to in vitro release studies. The control of these factors can be successfully used to modulate the release rate from matrices to show the effect of water soluble and water insoluble diluents. Comparative release results are shown in Figure 8. From the release profile the tablets containing MCC as diluent showed significant increase in the release of drug, this might be due to its swelling behavior of MCC in water and eventually disintegration of the tablets. Tablets contain mannitol and lactose as diluent showed significant higher drug release when compared with MCC and DCP. These might be due the rapid solubility of lactose and mannitol, tendency to form pores in the matrix which allow the dissolution medium to penetrate the matrix and dissolve the drug. These results may explain the slower release from rosin matrices containing MCC and DCP compared to those containing lactose or mannitol.

**Table 3.-** Post compression parameters of the formulated tablets.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Permissible limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm)</td>
<td>2.58 ± 0.34</td>
<td>---</td>
</tr>
<tr>
<td>Weight variation</td>
<td>3.42 ± 0.43</td>
<td>&lt; 5.0%</td>
</tr>
<tr>
<td>Hardness</td>
<td>4.4 ± 0.32</td>
<td>3.0 – 6.0 kg/cm²</td>
</tr>
<tr>
<td>Friability</td>
<td>0.66 ± 0.12</td>
<td>0.5 – 1.0 %</td>
</tr>
<tr>
<td>Drug content</td>
<td>98.92 ± 0.28</td>
<td>95.0 – 105.0 % w/w</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>98.53 ± 0.54</td>
<td>95.0 – 105.0 % w/w</td>
</tr>
</tbody>
</table>

**Table 4.-** Composition of diltiazem hydrochloride matrix tablet with different diluent.

<table>
<thead>
<tr>
<th>Ingredients(mg)</th>
<th>F7(1:1.75)</th>
<th>F8(1:1.75)</th>
<th>F9(1:1.75)</th>
<th>F10(1:1.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem Hydrochloride</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Rosin</td>
<td>157.5</td>
<td>157.5</td>
<td>157.5</td>
<td>157.5</td>
</tr>
<tr>
<td>Lactose.H₂O</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micro crystalline cellulose</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dicalcium Phosphate</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Mannitol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Tale</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

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Figure 3.- HPTLC chromatogram of diltiazem hydrochloride.

Figure 4.- HPTLC chromatogram of diltiazem hydrochloride: rosin (1:1).
Figure 5.- HPTLC chromatogram of matrix tablet formulation.

Figure 6.- *In vitro* release profile of diltiazem hydrochloride from matrix tablets.

Figure 7.- Comparison of in vitro release of optimized formulation and market formulation.
CONCLUSION

The study showed that rosin is an appropriate hydrophobic material that can be utilized as matrix forming agent to prolong the release of water soluble drug such as Diltiazem HCl. Preparation of matrices by direct compression was found to be more effective in controlling the release of drug. Release of drug from the matrices can be adjusted by using release enhancers like Lactose, Mannitol, MCC and DCP. Rosin is widely available in India, and is inexpensive. It can be used as substitute in place of currently marketed matrix forming polymers. The drug release from all the formulations mentioned above followed first order kinetics and the Higuchi model, thus indicating that there was no erosion of the matrix and the tablet maintained its surface area and shape.

BIBLIOGRAPHY


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