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Present peroral CDDS are designed for a maximum period of 24 h clinical efficacy. Such systems are primarily for drugs with short elimination half-life. However, drugs with longer half-lives also qualify as potential candidates for formulation into a CDDS, particularly when a reduction in the steady-state fluctuations in drug blood concentration is desired (Ritschel, 1989).

The ultimate goal of peroral CDDS is to achieve and to maintain a rather flat, plateau-like drug concentration in the blood at steady-state within a dosing interval, with minimal fluctuations between the maximum and the minimum steady-state drug levels. Hence, a prerequisite in the design of such delivery systems is the knowledge of a relationship between the desired pharmacological response, i.e., a well-defined therapeutic range and the pharmacokinetics of the drug. Only drugs for which such a relationship can be identified are a priori candidates for CDDS.

Development of CDDS is hindered by the inability to localise the dosage form in the selected regions of the gastrointestinal tract. It is in this regard that an increasing attention is being paid to the development of oral mucoadhesive drug delivery systems. It has been shown that it takes about 5 h for the tablets (administered orally) to arrive in the colon. Assuming that defecation in man occurs once or twice a day, the mean total gastrointestinal transit time is limited to about 16 h. Hence, even for 24 h duration CDDS, the time available for release might be limited to 16 h only and the remaining 8 h of the duration of the effect of the drug will largely be dictated by the elimination kinetics of the drug.

Chitosan, a natural polysaccharide, has shown great potential for microencapsulation and matrix systems by virtue of its mucoadhesive potential and negligible toxicity. Recently, chitosan has been shown to enhance the absorption of peptides across the gastrointestinal mucosa (Bernkop-Schnurch et al., 1997, 1998; Bernkop-Schnurch, 2000). In addition, chitosan is a promising candidate for colon-specific drug delivery (Tozaki et al., 1997; 1999a,b). Literature is replete with use of chitosan in conventional drug delivery both for sustained (Miyazaki et al., 1988) as well as fast release dosage forms (Upadrashita et al., 1992; Portero et al., 1998). Though, chitosan exhibits excellent compatibility with organic compounds, multivalent anions easily cross-link with it to form gels and precipitates. The cationic nature permits it to complex with oppositely
charged drugs/excipients, thereby altering the physicochemical characteristics of the formulation. However, when used alone, it results in higher friability, which can be reduced by the addition of various excipients as carbopol, citric acid etc. (Kristmundsdottir et al., 1995).

In the present investigation, we propose a matrix system for controlled drug delivery using nimesulide and diclofenac sodium as the model drugs in order to ascertain the potential of the polymer admixtures to modulate the release of the drug from the formulation. It was thought worthwhile, therefore, to undertake a research project involving matrix tablets prepared with a combination of polymers differing in their ionic characteristics, for controlled drug delivery. Of particular interest to the formulator is the comparative evaluation study of the drug release characteristics from such matrices and to quantify the differential release behaviour and specific formulation requirement.

The endeavour of the present research were to examine a wide range of polymers/combinations for various physicochemical parameters as swelling index, swelling rate and force of detachment from a biological membrane. Further, the ability of the polymers to complex in situ is also explored. In addition to the formulation development, the plan of the study also included:

- *in vitro* dissolution tests and effects of diluents on drug release,
- fitting of the release rate into mathematical models to ascertain the drug release pattern,
- investigating the ability of the polymers to reduce the ulcerogenic effects of diclofenac sodium in the rat model,
- performing *in vivo* bioavailability studies in human volunteers of the selected formulations, and to
- establish an *in vitro-in vivo* correlation.

Diclofenac sodium was chosen as a model drug because of its short elimination half-life (1-2 h), low dose (50-100 mg daily in divided doses), a feasible analytical procedure through spectrophotometry, high physicochemical stability, etc. The drug has a molecular weight of 318.13, a high partition coefficient (13.4), low solubility (> 9.0 mg/ml in distilled water and about 6.0 mg/ml in PB pH 7.2) and exhibits rapid absorption following oral administration.

Several studies have highlighted the advantages of SR diclofenac sodium over enteric coated formulation (Sahajwalla et al., 1991; Honorato et al., 1992).
On the other hand, nimesulide has a mean terminal half-life ranging between 1.8-4.73 h. The drug has a very poor aqueous solubility (0.01 mg ml⁻¹, distilled water), thereby leading to formulation problems and a variable bioavailability, \textit{in vivo}. Numerous studies have been performed to increase the aqueous solubility of the drug (Piel \textit{et al.}, 1997, Kapoor \textit{et al.}, 1998). However, as the gastric safety of nimesulide is dependent on the concentration of the drug achieved in the gastric mucosa (Jouzeau \textit{et al.}, 1997), an enhanced solubility of the drug from such formulations could result in an increased gastric irritation due to an elevated local drug concentration (Singla \textit{et al.}, 2000b). Besides, the lack of any \textit{in vivo} data, indicating lesser gastrointestinal toxicity for such formulations makes their use rather questionable.

Nimesulide conforms to the biopharmaceutic requirements essential for a drug to qualify for formulation into a CDDS (Table 31).

<table>
<thead>
<tr>
<th>Biopharmaceutic consideration</th>
<th>Parameter requirement*</th>
<th>Parameter for nimesulide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight/size</td>
<td>&lt;1000</td>
<td>308</td>
</tr>
<tr>
<td>Solubility</td>
<td>&gt;0.1 µg/ml (for pH 1.0-7.8)</td>
<td>5.0 µg/ml (pH 1.5); 15.0 µg/ml (pH 6.8); 10.0 µg/ml (distilled water)</td>
</tr>
<tr>
<td>Absorption mechanism coefficient</td>
<td>Diffusion</td>
<td>None reported, but the mechanism of absorption seems to be by passive diffusion</td>
</tr>
<tr>
<td>Apparent partition coefficient</td>
<td>High</td>
<td>6.4-6.8</td>
</tr>
</tbody>
</table>

*Ritschel, 1989

Taking into consideration the above biopharmaceutic and pharmacokinetic parameters, nimesulide seems to be an ideal candidate for formulating into a CDDS for once a day dosing, in order to improve patient compliance and to achieve a better and flatter drug plasma level profile.