The development of sustained-release formulations continues to be a great success for the pharmaceutical industry with much interest being shown by academic research. These formulations help to optimize the bioavailability and resulting blood concentration-time profiles of drugs. They were proved to increase patient compliance, reduce adverse effects, improve tolerability, increase therapeutic advantage and reduce healthcare cost.

Matrix technology is one of the most popular among the oral controlled drug delivery technologies owing to their simplicity, ease in manufacturing, high level of reproducibility, stability of raw materials and dosage form and ease of scale up and process validation (1). A matrix device, as the name implies, consists of drug dispersed homogeneously throughout a polymer matrix (2). Both hydrophilic and hydrophobic polymeric matrix systems are widely used to provide sustained delivery of drug substances. Drug release usually occurs by diffusion and/or erosion of the matrix system (3).

Hydrophilic matrices containing hydroxypropyl methylcellulose (HPMC) are a principal technology used for extended release (ER) oral dosage forms (4). HPMC, a semisynthetic derivative of cellulose, is a swellable and hydrophilic polymer. Matrix tablets prepared using HPMC on contact with aqueous fluids get hydrated to form a viscous gel layer on the matrix surface. This swelling and hydration properties of HPMC eliminate the burst release and act as physical and diffusion barrier to the rate of water penetration and the diffusional/erosional release of drug (5). HPMC displays good

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compression properties, can accommodate high drug loading and is considered non-toxic (6).

Diclofenac sodium (DS), sodium 2-(2,6-dichloroanilino)phenylacetate, one of the most useful pain killers, is a potent non-steroidal anti-inflammatory drug (NSAID), therapeutically used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. The anti-inflammatory activity of DS and most of its other pharmacological effects are related to the inhibition of the conversion of arachidonic acid to prostaglandins, which are mediators of the inflammatory process (7, 8). The conventional formulations containing 50 mg of DS are used in arthritis, spondylitis, post-operative pain management and other chronic inflammatory conditions. The dosing schedule is 3 to 4 times a day due to its short half-life (1-2 h). The extended release (ER) tablets of DS containing 75 or 100 mg of the drug are prescribed as once a day formulations. The major benefits of extended release DS tablets over conventional ones include reduced dosing frequency and decreased incidence of gastro-intestinal side effects (9). Hence, there is a strong rationale to develop extended-release oral formulation of DS.

Numerous studies have been carried out in order to achieve a desirable release rate of several NSAIDs to treat rheumatoid arthritis and osteoarthritis. HPMC hydrophilic matrices have been developed for the controlled delivery of DS employing different viscosity grades like HPMC K100LV (10) HPMC K4M (11, 12), HPMC K100M (10) and HPMC K15M (13). The latter study examined the use of HPMC K15M at a high concentration of approximately 50% w/w. In the recent study, a 3² full factorial design was conducted using polymer concentration at lower concentration range (10-30 % w/w) and compression force in the range (5-15 KN) to develop a sustained release formulation of DS. The optimum formulation was evaluated for the effect of diluent type and ratio, drug loading, drug solubility and polymer viscosity. The optimum formulation was found similar to the marketed product Voltaren® SR 75 mg. The stability behavior of the optimum formulation was studied according to the ICH guidelines.

<table>
<thead>
<tr>
<th>Table 1. Variables in 3² factorial design.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent variable</td>
</tr>
<tr>
<td>X₁</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y₁</td>
<td>Release efficiency (RE) (%)</td>
</tr>
<tr>
<td>Y₂</td>
<td>Mean dissolution time (MDT) (h)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Matrix of 3² full factorial design for tablet formulations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment no.</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>
EXPERIMENTAL

Materials

DS was kindly supplied by TABUK Pharmaceuticals (Tabuk, Saudi Arabia). Methocel® (HPMC) K15M (m.w. 10,000 Da) Premium CR grade was obtained from Colorcon (England). Granulac 200® (Lactose) was kindly supplied by Meggle Pharma (Wassenberg, Germany). Vivapur® PH 101 (microcrystalline cellulose) was purchased from JRS Pharma (Weissenborn, Germany). Kollidon® K30 (polyvinyl pyrrolidone) was kindly supplied from BASF, Germany. All other reagents were of pharmaceutical or analytical grade.

Methods

Experimental design

Two factors, three levels (3²) full factorial design were used to optimize polymer concentration (X1) and compression force (X2) using a statistical package Design-Expert 9 (Stat-Ease®, Inc.). Statistical models with interaction terms were derived to evaluate the effect of the two factors on tablet release efficiency (RE) (Y1) and mean dissolution time (MDT) (Y2). The selected two factors as well as their levels and analyzed responses are shown in Table 1.

The number of independent variables selected decides about the number of experiments that are to be performed (14). The matrix of the factorial design is represented in Table 2. Each row in the matrix identifies an experiment and each experiment provides a result (response). Also, the compositions of tablet formulations are represented in Table 3. This design provided an empirical bond order polynomial model. In this mathematical approach, each experimental response (Y) can be represented by a quadratic equation of the response surface:

\[ Y = B_0 + B_1X_1 + B_2X_2 + B_3X_1X_2 + B_4X_1^2 + B_5X_2^2 \]  

Preparation of the matrix tablets by wet granulation

Tablets were prepared by wet granulation as described in Table 3. Powders (batch size = 600 g) were sieved through...
a 0.630 mm mesh screen and mixed in a high shear mixer (chopper speed = 700 rpm, impeller speed = 200 rpm) for 20 min. A 20% PVP hydro-alcoholic solution (water : isopropanol, 10 : 90, v/v) was used as granulating fluid while mixing the powder bed in the high shear mixer (Chopper speed = 2500 rpm, impeller speed = 200 rpm, spray rate = 46 mL/min, wet massing = 5 min) to obtain the desired consistency of the mass. The wetted mass was sieved by passing it through a 1.25 mm mesh screen. Granules were dried in a hot air oven (Memmert, Tö80ul, Germany) at 40°C for 1 h. The residual solvent was determined using an infrared dryer (Mettler, LP16 Greifensee, Switzerland). The dried granules (residual solvent 2–3%) were passed through a 0.8 mm mesh screen. After sieving, 1% (w/w) magnesium stearate and 0.5% (w/w) colloidal silicon dioxide were added and mixed again in the high shear mixer (chopper speed = 400 rpm, impeller speed = 200 rpm) for 5 min. The 350 mg tablets were pressed in a rotary tableting machine (Rotab T, Kg-Pharma, Germany) with 10 mm concave punches at compression forces 5, 10 and 15 KN.

Characterization of the produced granules

Particle size

The size distribution of the prepared granules was investigated using laser light diffraction particle sizer (Mastersizer Scirocco 2000, Malvern Instruments, Grovewood Road, U.K.). For a typical experiment, about 2 g of granules were loaded in the sample micro feeder. All samples were analyzed 3 times and average results were registered. The sizes below 10% (d(0.1)), 50% (d(0.5)) and 90% (d(0.9)) of the granules were used to characterize the granule size distribution. The mean diameter was taken as the average of d(0.1), d(0.5), and d(0.9) values.

Bulk and tapped densities, Hausner’s ratio, compressibility index

Bulk density (BD) and tapped density (TD) were determined. Using Erweka SVM 102 tapped density tester, a sufficient quantity of granules from each formula was introduced into a 100 mL measuring cylinder. After recording the initial volume, the instrument worked according to USP method 1 (300 strokes/min; stroke height 15 mm). BD and TD, Hausner’s ratio and compressibility index were calculated.

Angle of repose

The fixed height funnel method was employed to determine the angle of repose of granules. Excess quantity of granules is allowed to drain through a funnel. The height of the funnel was fixed relative to the base. The granules were then allowed to flow through the funnel freely onto the surface and the diameter of the powder cone was measured.

Compression of the granules

The granules were compressed into tablets by an instrumented multiple press rotary tablet machine (Rotab T, Kg-Pharma, Berlin, Germany) using 10-mm diameter, round, standard concave punches. The tablets were collected during compression for in-process testing (weight and hardness) and were stored in airtight high-density polyethylene (HDPE) bottles pending further testing.

Characterization of the produced tablets

Weight variation

Twenty tablets from each batch were individually weighted on analytical balance (Mettler AJ150, USA). The average tablet weight and standard deviation (SD) were calculated (15).

Hardness

Tablet hardness was measured using hardness tester (Pharma test GmbH, Hainburg, Germany). The crushing strength of 10 tablets with known weight was recorded in Newtons (N). The average hardness and SD were calculated.

Thickness

The thickness in millimeters was measured individually for 10 pre-weighed tablets by using Mitutoyo digimatic caliper (Model CD-6 CSX, Kawasaki, Japan). The average tablet thickness and SD were computed.

Friability

Few tablets were selected from each batch and weighed to approx. 6.5 g. Each group of tablets was rotated at 25 rpm for 4 min in the friability apparatus (Electrolab EF-2 USP, India). The tablets were then reweighed to determine the loss in tablet weight. Friability was then calculated as percent loss in weight.

Drug content

Drug content uniformity of the prepared tablets was assessed according to USP requirements for content uniformity. Ten tablets were weighed individually, crushed and the drug was extracted with methanol. The solution was filtered, and the drug content was determined by injecting samples into a UPLC (Acquity® UPLC, Waters Inc., Bedford, MA, USA) with UV detection at 254 nm. Briefly, separa-
tion employed reverse-phase isocratic elution using a mobile phase consisting of 0.05 M acetate buffer (pH 2.5) and acetonitrile (50:50, v/v) run at flow rate of 0.5 mL/min and injection volume 1 µL. PDA detector was set to acquire 3D data from 210 to 280 nm while the 2D channel was recording at 254 nm. The column temperature was kept at 50°C while sample temperature was kept at 10°C. This method was employed in determination of DS content samples as well as dissolution samples (16). For dextromethorphan hydrobromide tablets, the content samples and the dissolution samples were analyzed spectrophotometrically at 278 nm against a linear calibration curve (r² = 0.999).

**In vitro drug release**

For poorly soluble drugs, medium selection for dissolution tests is an important step in method validation due to the difficulty to achieve sink condition, which is defined as the volume of medium at least three times greater than that required to dissolve the dose of the drug being tested (17). DS has a pH-dependent solubility and consequently exhibits an extremely low solubility in acidic media (18), whereas it is soluble in water and basic media. The phosphate buffer pH 7.5 was used for dissolution as stated in the USP 32 monograph for the extended release tablets of DS. The drug has a solubility of 5.15 mg/mL in the employed phosphate buffer (pH 7.5) which maintained the sink conditions for the dissolution of DS (19).

**In vitro dissolution tests** were carried out using USP 24 dissolution rate test apparatus Type II (paddle type) (LOGAN Instrument Corp., Somerset, NJ). The dissolution medium was 0.05 M phosphate buffer (pH = 7.5) for 24 h (900 mL, 37°C) at 50 rpm. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with freshly prepared dissolution medium. The samples were filtered, and analyzed by injection into UPLC or spectrophotometrically as mentioned above in the previous section. Dissolution tests were performed in triplicate and the mean value of the cumulative % or amount drug release was plotted against the time interval.

**Modeling of the release data**

**Model-dependent approaches**

To elucidate the mechanism of drug release from these formulations, the data were fitted to zero order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs. time), Higuchi’s (cumulative percentage of drug released vs. square root of time), and Korsmeyer’s (log cumulative percentage of drug released vs. log time) equations (20):

- Zero order equation,
  \[ f_t - f_i = K_0 t \]  
  where \( f_i \) is the initial quantity of drug, \( f_t \) is the fraction dissolved at time \( t \) and \( K_0 \) is the zero order rate constant.
- First-order equation,
  \[ \log Q_t = \log Q_0 - K_1 \times t \div 2.303 \]  
  where \( Q_t \) is the amount released at time \( t \), \( Q_0 \) is the initial amount of drug in solution and \( K_1 \) is the first order rate constant.
- Higuchi’s equation,
  \[ F_t = K_{H} t^{2/3} \]  
  where \( F_t \) is the fraction dissolved at time \( t \) and \( K_H \) is the Higuchi dissolution constant.
- Korsmeyer et al. equation (Power law),
  \[ \frac{M_t}{M_{\infty}} = K \times t^{n} \]  
  where \( M_t \) is the amount of drug released at time \( t \), \( M_{\infty} \) is the amount of drug released after infinite time, \( K \) is the Korsmeyer’s dissolution rate constant and \( n \) is the release exponent, indicative of the drug release mechanism. Korsmeyer-Peppas model is expected to be valid up to ~60% cumulative drug released, so the data were restricted to that range (21). In case of Fickian release (diffusion-controlled release), \( n \) has the limiting values of approximately 0.45 for release from cylinders, whereas it has a value of approximately 0.89 for case II transport (relaxation-controlled release) from cylinders. The non-Fickian release (anomalous transport of drug) occurs when the \( n \) values fall between the limiting values of Fickian and case II transport, i.e., 0.45-0.89. The non-Fickian kinetics corresponds to coupled diffusion/polymer relaxation.

**Model-independent approaches**

The model independent parameters such as RE and MDT were calculated (20). RE is defined as the area under the dissolution time curve up to a certain time, \( t \), expressed as the percentage of the area of the rectangle described by 100% dissolution in the same time. The MDT values were calculated by the following equation:

\[ MDT = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \]  

where \( j \) is the sample number, \( n \) is the number of dissolution sample times, \( t_j \) is the time at midpoint between \( t_{j-1} \) and \( t_j \) (easily calculated with the expression \((t_{j-1} + t_{j})/2\)), and \( \Delta M_j \) is the additional amount of drug released between \( t_j \) and \( t_{j-1} \).

In order to compare dissolution profiles of DS, the similarity factor (\( f_2 \)) was calculated as follows (22):
where \( n \) is the number of time points, \( R \) is the dissolution value of the reference at time \( t \), and \( T \) is the dissolution value of the test time \( t \).

**Statistical analysis**

The mean values (\( n = 3 \)) were subjected to one-way analysis of variance (ANOVA) to examine the statistical difference using Design Expert-9 software (Stat-Ease\textsuperscript{®}, Inc., Minneapolis, USA). The software performs the individual analysis of responses and calculates the sum of squares (SS), mean square (MS), Fischer’s ratio (F statistics) and p value. The F statistics and p value give the significance level of each term, considering the null hypothesis (\( H_0 \)) is true. The terms with a p value less than 0.05 are considered significant at a level of significance \( \alpha = 0.05 \). When the F value obtained is greater than the critical F value from the F distribution table, the factor becomes significant and the null hypothesis is rejected.

**Differential scanning calorimetry (DSC)**

DSC was carried out for the pure drug, HPMC K15M and their physical mixture. Samples (3-5 mg) were hermetically sealed in aluminium pans and heated at a constant rate of 10\(^{\circ}\)C/min over a temperature range of 25–320\(^{\circ}\)C (23). Thermograms of the samples were obtained using differential scanning calorimeter (DSC-60, Shimadzu, Japan). Indium standard was used to calibrate the DSC temperature and enthalpy scale. \( N_2 \) was used as a purging gas at rate of 40 mL/min.

### Table 4. Characterization of the prepared granules.

<table>
<thead>
<tr>
<th>Measured parameter</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean particle size (µm)</td>
<td>436.57</td>
<td>303.76</td>
<td>315.03</td>
<td>443.65</td>
<td>379.58</td>
<td>120.59</td>
<td>327.48</td>
<td>616.45</td>
<td>348.4</td>
<td>360</td>
</tr>
<tr>
<td>Angle of repose ((^{\circ}))</td>
<td>34.01</td>
<td>34.69</td>
<td>35.77</td>
<td>32.88</td>
<td>31</td>
<td>32.71</td>
<td>32.18</td>
<td>31.53</td>
<td>30.19</td>
<td></td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
<td>0.51</td>
<td>0.44</td>
<td>0.4</td>
<td>0.39</td>
<td>0.52</td>
<td>0.47</td>
<td>0.47</td>
<td>0.44</td>
<td>0.46</td>
<td>0.48</td>
</tr>
<tr>
<td>Tapped density (g/mL)</td>
<td>0.65</td>
<td>0.51</td>
<td>0.51</td>
<td>0.49</td>
<td>0.65</td>
<td>0.55</td>
<td>0.56</td>
<td>0.54</td>
<td>0.54</td>
<td>0.58</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.28</td>
<td>1.16</td>
<td>1.27</td>
<td>1.26</td>
<td>1.25</td>
<td>1.18</td>
<td>1.14</td>
<td>1.12</td>
<td>1.17</td>
<td>1.21</td>
</tr>
</tbody>
</table>

### Table 5. Physical characterization of designed controlled release matrix tablets of diclofenac.

<table>
<thead>
<tr>
<th>Formulations*</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug content (% of LC) (RSD\textsuperscript{®})</td>
<td>96.98  (1.75)</td>
<td>96.32  (0.93)</td>
<td>95.54  (2.68)</td>
<td>98.96  (1.51)</td>
<td>100.76 (1.16)</td>
<td>100.73 (0.88)</td>
<td>93.92  (1.97)</td>
<td>102.37 (4.26)</td>
<td>97.02  (3.02)</td>
<td>96.12  (2.86)</td>
</tr>
<tr>
<td>Tablet weight (mg) ± SD</td>
<td>351.96 (± 4.4)</td>
<td>350.94 (± 6.4)</td>
<td>348.64 (± 2.7)</td>
<td>352.89 (± 3.6)</td>
<td>351.68 (± 3.1)</td>
<td>350.45 (± 3.1)</td>
<td>352.9 (± 3.5)</td>
<td>352.36 (± 3.9)</td>
<td>350.91 (± 4.6)</td>
<td>349.27 (± 4.6)</td>
</tr>
<tr>
<td>Hardness (N) ± SD</td>
<td>99.9   (± 3.9)</td>
<td>98.7   (± 7.6)</td>
<td>95.8   (± 3.7)</td>
<td>94     (± 3.4)</td>
<td>77.5   (± 5.3)</td>
<td>84.5   (± 2.4)</td>
<td>76.2   (± 4.4)</td>
<td>117.1  (± 7.6)</td>
<td>69.7   (± 4.2)</td>
<td>74.9   (± 3.2)</td>
</tr>
<tr>
<td>Thickness (mm) ± SD</td>
<td>4.54   (± 0.03)</td>
<td>4.73   (± 0.03)</td>
<td>4.86   (± 0.02)</td>
<td>4.73   (± 0.01)</td>
<td>4.59   (± 0.03)</td>
<td>4.57   (± 0.04)</td>
<td>4.57   (± 0.02)</td>
<td>4.6    (± 0.03)</td>
<td>4.67   (± 0.03)</td>
<td>4.54   (± 0.04)</td>
</tr>
<tr>
<td>Friability* (% loss)</td>
<td>0.09</td>
<td>0.1</td>
<td>0.2</td>
<td>0.01</td>
<td>0.08</td>
<td>0.09</td>
<td>0.1</td>
<td>0.06</td>
<td>0.03</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*All formulations were compressed at 15 KN; ' LC stands for label claim; ' RSD stands for relative standard deviation; ' Amount of tablets weighed equivalent to 6.5 g.
Fourier transform infrared absorption spectroscopy

The infrared (IR) spectra of pure DS, polymer and their physical mixture (1:1) were performed using Shimadzu IR-470 spectrophotometer (Tokyo, Japan). The samples were prepared as KBr disks compressed using a hydraulic press under a pressure of 6 ton/cm². Scanning was performed at a wave number range of 600-4000 cm⁻¹. In addition, IR studies were conducted for F1 tablet formulation to detect any interaction that might occur during processing. The data were analyzed using IR Solution software (version 1.10).

X-ray diffraction pattern

Powder X-ray diffraction patterns of the drug, polymer and their physical mixture were carried out using a wide-angle X-ray diffractometer (Rigaku Ultima IV X-Ray Diffractometer, Japan). The instrument was operated to conduct full scan (2θ ranging from 0° to 150°) with the counts being accumulated for 1 s after each step (24).

Batch reproducibility and stability on storage

Six batches of the optimum formulation were prepared and their quality and respective in vitro release characteristics were evaluated under the same conditions to determine the batch reproducibility. The optimum formulation was stored in closed containers in stability cabinet (Binder GmbH, Tuttlingen, Germany) at 25 ± 2°C and 60 ± 5% relative humidity (RH) for 12 months, 30 ± 2°C and 65 ± 5% RH for 6 months and 40 ± 2°C and 75 ± 5% RH for 6 months. Physical characteristics and release profiles of the formulation were studied for the effect of storage.

RESULTS AND DISCUSSION

Physical characterization of the granules

The granules of different formulations and drug powder were evaluated for angle of repose, bulk densities, Hausner’s factor and compressibility index. The results of angle of repose (30-35°) indicate good flow properties of the prepared granules. This was further supported by lower Hausner’s ratio and compressibility index values (Table 4). Hausner’s ratio showed that powders with low inter-particle friction had ratios of approximately 1.2. Further, compressibility index values up to 20% result in good to excellent flowability and compressibility. The mean particle size for the formulations ranged between 120-616 µm according to differences in the percentage and/or particle characteristics of the individual components.

Physical characterization of the produced tablets

The physical appearance, tablet hardness, friability, weight variation and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 5. Tablet hardness was found to be between 69 and 117 N and friability was less than 0.1% (w/w). The manufactured tablets showed acceptable weight variation and drug content uniformity, indicating that the employed wet granulation conditions are acceptable for preparing good quality matrix tablets of DS.

In vitro drug release studies

In vitro drug release from matrix systems depends on several factors, such as the manufacturing process, the type of excipient, drug solubility and concentration, polymer concentration and pH of the dissolution medium (25).

The HPMC matrix undergoes rapid gelification in water. It becomes hydrated in contact with water forming a gel layer in which the polymer passes from the crystalline state to a rubbery state due to the increase in size of the polymer molecules. The transport phenomena that take place through this gel layer include the entry of the aqueous medium, the exit of the drug to the outside of the system and matrix erosion. As more water enters the system, the thickness of the gel layer increases. In the interim, the surface-most polymer chains, which become hydrated earlier, gradually relax until they lose consistency, after which matrix erosion begins (6).

The release of DS form HPMC tablets was reported to follow a non-Fickian release mechanism (6). In relation to the exponent (n) derived from Eq. (6), all the means were in the range 0.45–0.89, a value that indicates both diffusion and erosion mechanisms are occurring in the matrices. The dissolution data, plotted as the percentage DS dissolved till 60% versus square root of time (26), gave typical straight line plots and correlation coefficients ($r^2$) between 0.981 and 0.998. Generally, this release will vary with the square root of time according to the following equation:

$$M_t = A \left[ DC_0 (2C_s - C_0) t \right]^{1/2}$$

where $M_t$ is the total mass released up to time $t$; $A$ is the total area of a two-sided slab; $C_0$ is the initial drug concentration, $C_s$ is the solubility of the drug in the polymer, and $t$ is the time. Although matrix swelling involves an increase in the surface area of the system, which favors drug release, the resistance to drug diffusion through the gel layer is stronger, which means that drug release will decrease with time (3).
Effect of compression force and polymer concentration (F1, F2 and F3)

The measured responses RE “Y1” and MDT “Y2” are represented in Table 6 for the independent variables polymer concentration “X1” and compression force “X2”. The derived equations for the analysis for each response variable were:

\[
Y_1 = 104.7 - 1.26X_1 - 1.28X_2 + 0.04X_1X_2 \quad (10)
\]

\[
Y_2 = 0.86 + 0.19X_1 + 0.15X_2 \quad (11)
\]

The above equations were derived by the best-fit method to describe the main effect of process variables (X1 and X2) and their interaction (X1X2) on the responses (Y1 and Y2). The values of the coefficients (regression coefficient) for X1 and X2 are associated with the effect of these variables on the response. Coefficients with more than one factor represent an interaction effect of both factors (e.g., X1X2). A positive sign reflects a synergistic effect while a negative sign stands for an antagonistic effect.

From the regression equations 10, 11, it could be seen that both variables (X1 and X2) had a noticeable, significant (F = 67.17, p < 0.05) antagonistic effect on RE (Y1) and significant (F = 70.15, p < 0.05) synergistic effect on MDT (Y2) of the formulations. There was a noticeable significant (p < 0.05) interaction effect (X1X2) on the measured response Y1, whereas no noticeable interaction effect (X1X2) on the measured response Y2.

Figure 1 depicts the dissolution profiles of a formulation compressed at the three different com-
pression forces (5, 10 and 15 KN). The independence of the DS release from this variable is shown especially at a high concentration. Once the polymer was swollen, the dissolution profiles became similar to those tablets compressed to a higher crushing strength. However, tablets made at the lowest concentration (F1) with HPMC K15M showed an initial burst effect at compression force 5 KN due to a partial initial disintegration. This behavior disappeared at higher concentration where F3 did not show any significant effect of compression force. The effect of compression force on RE and MDT is less pronounced than that of polymer concentration. Although compression force is a statistically significant factor in tablet hardness, its effect on drug release from HPMC tablets is minimal (27). In general, compression force may affect the porosity of the tablets; however, the porosity of the hydrated matrix is independent of the initial porosity (28). As a result, the compression force seems to have little influence on drug release.

It has been reported that an increase in the percentage of polymer elicits a greater degree of cross-linking of the polymer side chains, which in turn increases the viscosity of the gel and its tortuosity and increases the diffusional path length, which are the main characteristics that prevent the diffusion of the drug through the gel (29). Although this may result in a decrease in the effective diffusion coefficient of the drug and consequently a reduction in the drug release rate, diffusion is not the only mechanism that governs release from HPMC matrices. Erosion of the matrix itself following hydration of the HPMC will contribute to the overall release (30). Interestingly, F1 showed no significance difference (p < 0.05) regarding the values of RE (80.75%) and MDT (5.02 h), Table 6, as compared to Voltaren® SR 75 mg with comparable values for RE and MDT where the values were 78.67%, 5.8 h and 76.69%, 6.4 h for both formulations, respectively, as described in Table 6. The sustained release properties were not affected after the dose increment, which may be due to the low solubility of DS. Besides, increasing the dose from 75 to 100 mg is not considered to be too much dose increment. This is considered an advantage for the developed formulation where it showed flexibility with increasing the drug load while retaining the sustained release properties of the dissolution profile.

Effect of diluent type and ratio (F1, F4, F5 and F6)

Although diluents are normally thought of as inert ingredients, they can significantly affect the biopharmaceutical, chemical, and physical properties of the final tablet. The effect of diluent type and ratio on the drug release rate has been reported (31). In general, an increase in the amount of diluting agents in matrix formulations involves an increase in the drug release rate (29). Figure 2 shows the dissolution profiles of the formulations F1, F4, F5 and F6. Altering the proportion of lactose and MCC as in F4 resulted in a noticeable non-significant (p > 0.05) decrease in drug release. F4 showed a RE value of 79.06% and MDT value of 5.45 h with $f_2$ value 80.72 as compared to F1. The slight decrease in the drug release can be explained by the fact that F4 contains fewer amounts of lactose (soluble part) and more of MCC (insoluble part) than F1, and as a result less water penetration and slower rate of drug dissolution and diffusion. However, in F5 using mannitol instead of lactose with the same percentage resulted in a significant increase (p < 0.05) in the release profile where the RE and MDT values became 87.39% and 4.14 h, respectively, with similarity factor $f_2 = 43.6$. Mannitol has slower dissolution kinetics than lactose, however, the drug release was faster due to the fact that mannitol disintegrates whereas lactose dissolves rather than disintegrates forming a viscous layer on the surface of the tablet which slows down the penetration of water (32). After reversing the proportion of mannitol and MCC as in F6 i.e., increasing the insoluble portion in the formulation, the RE decreased again to 84.4% while MDT increased to 5.27 h and the similarity factor between F6 and F1 increased to $f_2 = 69.3$.

Effect of drug loading (F1 and F7)

Increasing the drug load or dose would be considered as a challenge for developing a sustained release hydrophilic matrix if the drug is a highly water soluble compound (6). However, after increasing the dose from 75 to 100 mg, the formulation F7 retained the sustained release properties of the release profile as shown in Figure 2. Also, F7 showed a similar ($f_2 = 70.67$) dissolution profile to Voltaren® SR 100 mg with comparable values for the RE and MDT where the values were 78.67%, 5.8 h and 76.69%, 6.4 h for both formulations, respectively, as described in Table 6. The sustained release properties were not affected after the dose increment, which may be due to the low solubility of DS. Besides, increasing the dose from 75 to 100 mg is not considered to be too much dose increment. This is considered an advantage for the developed formulation where it showed flexibility with increasing the drug load while retaining the sustained release properties of the dissolution profile.

Effect of drug solubility (F1 and F8)

The release rate is affected by the drug solubility (33). The release of DS and dextromethorphan hydrobromide from HPMC matrix tablets is affected by their solubilities in different pH media. While DS has a pH dependant solubility i.e., poorly soluble in...
acidic pH and freely soluble in alkaline pH, dextromethorphan hydrobromide is soluble in both pH media. The release profiles of the two drugs from the matrix are comparable to each other with $f_2$ value of 81.49 when the dissolution is tested at pH 7.5 as shown in Figure 2. However, the release rate of dextromethorphan was faster than that of DS when studying the drug release during pH shift (pH 1.2 then pH 7.5) due to their difference in solubility in acidic pH. In acidic pH, DS particles embedded within the matrix network do not solubilize and as a result solvent penetration becomes difficult and formation of gel layer is minimal for the entire acidic stage or even delayed till the alkaline stage. This results in a small percent of release of approx. 2% after 2 h for F1, which might be due to surface erosion. In contrast, dextromethorphan being soluble in acidic pH, dissolves rapidly from the surface of the matrix showing a burst effect and allowing for solvent penetration and rapid formation of the gel layer through which drug release resumes by diffusion. Some authors attributed this case to the fact that the drug itself would form microcavities in the gel layer, through which it is able to access the dissolution medium (6).

Effect of polymer viscosity

The polymer viscosity is one of the parameters that controls drug release and determines the mech-
The release characteristics from the formulations were studied by varying formulation and processing parameters. The swelling and erosion percentages are dependent upon the viscosity of the polymer (34). As the viscosity of the polymer increases, the percentage of swelling increases and the percentage of erosion decreases forming a stronger gel, which decreases the drug release rate. Methocel® containing formulations, namely HPMC K15M, HPMC K4M, and HPMC K100LV, were compared for the rate of drug release. The RE was highest (98.21%) in case of F10 (lowest viscosity) and lowest (80.75%) in case of F1 (highest viscosity). This is explained by the greater ability of more viscous polymers to capture water causing rapid swelling of the polymer, and hence, a stronger gel is formed. The faster rate of drug release observed with lower viscosity grades of HPMC can be attributed to less polymer entanglement, less gel strength, and to the larger effective molecular diffusion area at lower viscosity compared with higher viscosity grades of HPMC (35).

DSC, FT-IR, and XRD studies

Differential scanning calorimetry (DSC), FT-IR, and X-ray powder diffraction (XRPD) experiments were engaged for inspection of crystallinity properties as well as scrutinizing any possible interactions between drug and carrier in the prepared formulations. DSC thermograms of pure drug, HPMC K15M, and physical mixture are demonstrated in Figure 3A. Some changes or modifications in shape, peak temperature may arise simply from mixing of the components (36). Therefore, these changes or modifications were not considered in determining compatibility of the excipient with the drug. Appearance of new peaks or disappearance of DS endotherm or major shift in the peak temperature was major criteria in determining compatibility of respective excipients with the drug.

The DSC curve of DS was typical of a crystalline anhydrous substance as shown in Figure 3A. According to the figure, three peaks appeared in the DSC thermograms of pure DS. The first peak (28.5°), an exothermic peak pointed to position of the peaks. This result is in agreement with studies of Ranjan et al. (23). All exothermic peaks prior to an endothermic peak correspond to the melting point of DS.

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>Voltaren® SR 75 mg</th>
<th>Voltaren® SR 100 mg</th>
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<tbody>
<tr>
<td>Zero order</td>
<td>0.973</td>
<td>0.956</td>
<td>0.949</td>
<td>0.914</td>
<td>0.893</td>
<td>0.955</td>
<td>0.932</td>
<td>0.966</td>
<td>0.942</td>
<td>0.984</td>
<td>0.97</td>
<td>0.978</td>
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<tr>
<td>First order</td>
<td>0.782</td>
<td>0.709</td>
<td>0.699</td>
<td>0.709</td>
<td>0.609</td>
<td>0.76</td>
<td>0.695</td>
<td>0.719</td>
<td>0.754</td>
<td>0.829</td>
<td>0.835</td>
<td>0.803</td>
</tr>
<tr>
<td>Higuchi model</td>
<td>0.998</td>
<td>0.993</td>
<td>0.993</td>
<td>0.987</td>
<td>0.987</td>
<td>0.99</td>
<td>0.981</td>
<td>0.997</td>
<td>0.984</td>
<td>0.993</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Korsmeyer-Peppas model</td>
<td>0.623</td>
<td>0.629</td>
<td>0.545</td>
<td>0.559</td>
<td>0.59</td>
<td>0.683</td>
<td>0.639</td>
<td>0.694</td>
<td>0.631</td>
<td>0.753</td>
<td>0.45</td>
<td>0.55</td>
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<tr>
<td>RE %</td>
<td>80.75</td>
<td>71.88</td>
<td>67.32</td>
<td>79.06</td>
<td>87.39</td>
<td>84.4</td>
<td>78.67</td>
<td>78.9</td>
<td>89.56</td>
<td>98.21</td>
<td>83.5</td>
<td>76.69</td>
</tr>
<tr>
<td>MDT h</td>
<td>5.02</td>
<td>7.39</td>
<td>8.46</td>
<td>5.45</td>
<td>4.14</td>
<td>5.27</td>
<td>5.8</td>
<td>5.08</td>
<td>3.99</td>
<td>1.78</td>
<td>4.91</td>
<td>6.4</td>
</tr>
<tr>
<td>$f_2$</td>
<td>65.01</td>
<td>45.06</td>
<td>30.39</td>
<td>80.72</td>
<td>43.6</td>
<td>69.3</td>
<td>70.67</td>
<td>81.49</td>
<td>49</td>
<td>23.47</td>
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<td></td>
</tr>
</tbody>
</table>

* Formulations were compressed at 15 KN. † Calculated for the first 60% drug release.
responding to melting of the drug suggesting oxidation (decomposition) of DS before reaching its melting point (37). A large broad endothermic effect, over the temperature range 50 to 100°C, was observed for HPMC K15M (Fig. 3B), upon evaporation of adsorbed water (38) and it did not show any melting endotherm.

DSC was carried out for their physical mixture in the ratio 1 : 1 (w/w). This ratio was chosen, because it maximizes the likelihood of observing any interactions (39). The combination of the drug with the polymer, DS/HPMC K15M (Fig. 3C) demonstrated a disappearance of the drug endotherm. This may be considered as a strong solid phase interaction between the components. The miscibility between the components seems to occur in a large extension. In general, the thermograms of solid state drug/excipient mixtures allow the detection of interactions between the components. However, some authors recognize that the occurrence of physical or chemical interactions does not necessarily indicate an incompatibility (40). Additionally, they agree that a change observed in the DSC curves is an unambiguous proof of interaction between drug and excipients.

The binary mixture was further evaluated with FT-IR and XRD studies to determine the true nature of the interaction. FT-IR spectra of the samples are shown in Figure 4. The FT-IR absorption bands in the region of 3500 cm⁻¹ were attributed to OH group as well as to the N–H (amine group) stretching vibration. The band at 1575.06 cm⁻¹ for DS was assigned to the C=O stretching vibration for carbonyl groups, and the bands from 1453.52 and 1398.11 cm⁻¹ correspond to the scissoring vibration of the CH₂ group adjacent to the carbonyl. The doublet from 1305.04 and 1282.36 cm⁻¹ corresponds to C–O stretching band, as well as to C–N stretching absorption, together with C–H bend (in plane) from aromatic ring. The strong bands from 766.47, respectively 747.03 cm⁻¹ correspond to the out-of-plane C–H bend (41). FT-IR spectra of the binary mixture and the formulation F1 (ground tablet) retained all characteristic bands of the drug indicating there was no change in structure of the drug. It also did not show any new bands indicating that HPMC K15M was compatible with the drug. Results obtained in DSC studies could be explained on the basis of amorphization of the drug. Amorphization involves formation of crystalline micro aggregates of the drug and their considerable dispersion within the amorphous HPMC.

The X-ray diffraction patterns for DS, HPMC K15M, physical mixture and ground tablet (F1) are shown in Figure 5. The crystalline nature of the drug was clearly demonstrated by the characteristic XRPD pattern with peaks appearing at 6.3, 6.7, 8.5, 11.2, 15.2, 17.2, 19.9, 27.1, 27.9 and 37.9 2θ values. These results are in accordance with data reported previously (37). Obviously, there was no significant change for XRD curve for DS in the binary mixture and the ground tablet (F1). Reduced height of the drug peaks may be due to dilution effect of the drug in the carrier. No notable crystallinity change was also observed indicating compatibility of the drug and the polymer.

**Batch reproducibility and stability on storage**

No significant difference was observed in the release profile of different batches of each matrix tablet formulation of DS, indicating that the manufacturing process employed was reliable and reproducible. The whole assessment of the stability of the
dosage form depends on the collective results obtained from the effect of the three conditions. According to the ICH guidelines, if long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and “significant change” occurs at any time during 6 months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria (42). The release kinetics and physical characteristics were unaltered for up to 1 year of storage in long term conditions or 6 months in the intermediate conditions. However, in the accelerated term conditions a significant increase in tablet weight and hardness was observed due to water uptake by HPMC. Also dimensions of the tablets were altered where thickness increased due to polymer swelling and the drug release increased significantly in these conditions. The stability data are presented in Table 7. The observed stability data suggests that DS was stable in HPMC matrices.

**CONCLUSION**

HPMC matrix tablets of DS were successfully prepared using wet granulation method. There were several formulation variables affecting the properties of DS release, including polymer concentration, diluent type and ratio, drug loading, drug solubility and polymer viscosity. Adjusting the previous factors is essential for attainment of successful stable sustained release formulation. Nature and ratio of diluent may enhance or retard release rate. Increasing polymer concentration and viscosity were shown to have an antagonistic impact on drug release. Compression force had a minimal effect on drug release. The drug solubility, especially pH dependent solubility, should be taken in consideration while monitoring the release characteristics. Drug-polymer interaction studies did not show any incompatibility. The HPMC matrix tablet F1 matched to the release profile of the marketed product Voltaren® SR 75 mg. This formulation approach offered an attractive alternative towards once a day tablet formulation of the drug.

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**Declaration of interest**

All the authors declare that there is no conflict of interest.

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