Modulation of in-vitro drug-release from a HPMC matrix system: potential role of a disintegrant
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Abstract
Purpose: The objective of the current study was to investigate the role of disintegrants in modulation of drug release from HPMC-based hydrophilic matrices. Methods: The polymer matrices of a water-soluble drug, Propranolol hydrochloride, were prepared in combination with different disintegrants by wet-granulation approach. The widely used superdisintegrants like crospovidone (CP), croscarmellose sodium (CCS), calcium carboxymethyl cellulose (CaCMC) and sodium starch glycolate (SSG) were investigated for their potential role as release modifiers. The polymer-disintegrant combinations were evaluated for in-vitro drug-release behaviour at various pH conditions coupled with determination of swelling behaviour and gel properties of matrices through texture analysis. Results: The polymer-disintegrant combinations provided control over initial release rate and also exhibited complete drug release over 24 h. The work of penetration of hydrogels after 24 h dissolution study revealed that formulation with croscarmellose sodium showed complete relaxation of gel which fostered the complete drug release. Drug-release from the developed combination matrices was observed to be primarily Fickian diffusion based, except for combination of HPMC- sodium starch glycolate based matrices, where non-Fickian behaviour was observed. Barring sodium starch glycolate, all other polymer-disintegrant combinations provided pH-independent drug release. The accelerated stability studies of optimized HPMC-disintegrant matrix system were also satisfactory. Conclusions: The results of this study suggest that a suitable disintegrant when used in combination with HPMC, could modulate the drug-release and also synergize the release-controlling properties of hydrogel matrix systems. These findings can certainly be applied to develop controlled-release hydrogel matrix system of other highly water-soluble drug candidates, and hold a great potential in development of cost-effective and stable HPMC-matrix systems with customized drug-release behaviour.

Keywords: Propranolol hydrochloride, hydrophilic matrices, swelling, disintegrant, release kinetics.

Introduction
Hydrogels are three dimensional, hydrophilic, polymeric networks capable of swelling in water or biological fluids, and retain a large amount of fluid in the swollen state [1,2]. The unique physical properties of hydrogels are because of their highly porous structure that can be modified by controlling the density of cross-links in the gel matrix and their affinity for the aqueous environment in which they swell. Their porosity permits loading of drugs into the gel matrix and release drug at a rate dependent on the diffusion coefficient of the small molecule or macromolecule, through the gel network [3].

Hydroxypropyl methylcellulose (HPMC), the propylene glycol ether of methylcellulose and a water soluble nonionic polymer, is widely used excipient for formation of hydrophilic matrix [4]. The drug release mechanism and kinetics of hydrophilic matrix system is primarily based on aqueous solubility of drug substance and the swelling and erosion properties of the polymer [5,6]. Combination of anionic and non-ionic polymers has been employed widely to control the drug release [7-9]. Further, polymer combination with disintegrants, are also reported wherein the presence of a disintegrant has been shown to modulate drug release in HPMC-disintegrant combination matrix [10,11].

Disintegrants are indispensable class of excipients for solid oral dosage forms, which aid in tablet disintegration and thus help in release of active ingredient(s) from the dosage form. Disintegrants function by several mechanisms like swelling, wicking or particle repulsion. Swelling is the most widely accepted functional mechanism for disintegration as almost all disintegrants show swelling to some extent [12].

In the current study, four different disintegrants Carboxymethylcellulose calcium (CaCMC), Crospovidone (CP), Croscarmellose sodium (CCS) and sodium starch glycolate (SSG) with different functional mechanisms were studied in combination with HPMC to explore their potential as release modulator from the prepared hydrogel matrix. The key objective was to investigate the effect of these different disintegrants on the drug release...
mechanism from developed HPMC based matrix systems. Propranolol Hydrochloride, a BCS class I antihypertensive drug, known for its non-selective β-adrenergic blocking activity and short plasma half-life (3-5h), was selected as a model drug candidate for these investigations [13]. CaCMC is a calcium salt of poly-carboxymethyl ether of cellulose and it swells several times to that of its original bulk when comes in contact with water. CP is a water insoluble synthetic cross linked homopolymer of N-vinyl-2-pyrrolidinone. It acts as a disintegrant because of its high capillary activity, hydration capacity and little gel forming tendency. CCS is the sodium salt of a cross linked, partly O-(carboxymethylated) cellulose, and SSG is the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch. It acts as a disintegrant because of its wicking and swellable nature [14,15].

Materials and Methods

Materials

Propranolol Hydrochloride was obtained from Dr. Reddy’s Laboratories Limited, Hydroxypropyl methylcellulose (HPMC K100M) was purchased from Dow Chemical, USA, and Calcium Carboxymethylcellulose; E.C.G-505 (CaCMC) was a gift sample from Fenwest, IA. Crospovidone (Kollidon® CL) was purchased from BASF, Mumbai, India. Croscarmellose sodium (Ac-Di-Sol) was purchased from FMC biopolymer India. Sodium starch glycolate (GLYCOLIS®) was a gift sample from Roquette India Private Limited, Mumbai, India. Di-basic calcium phosphate (A-Tab®) was purchased from Innophos USA. Povidone K-30 (PVP K-30) was purchased from ISP (India) Pvt. Limited, Mumbai. Colloidal silicon dioxide (Aerosil 200) was obtained from Degussa Evonik AG, Germany and Magnesium stearate was purchased from Mallinckrodt Specialty Chemicals, Louis, MO, USA. All other solvents and chemicals used were of analytical grade.

Methods

Preparation of matrix tablet

Propranolol Hydrochloride, HPMC K100M and the disintegrant (CaCMC, Crospovidone, Croscarmellose sodium or Sodium starch glycolate) were accurately weighed and sifted through #40 mesh ASTM. The binder solution of PVP K-30 in Isopropyl alcohol (IPA) was prepared. Wet granulation was performed in high shear mixer granulator (HSMG) (M/s. Saral Engineering) with two minutes of binder addition time and one minute kneading time. The granules were dried in rapid drier (Retsch TG 200) at 40°C for 30-40 minutes until loss on drying was observed to be less than 2%w/w. The dried granules were passed through #25 ASTM mesh and then mixed with Dicalcium phosphate and Colloidal silicon dioxide (Aerosil) which were earlier sifted through #40 mesh ASTM. The final blend was lubricated with Magnesium stearate (# 60 mesh sifted in a suitable blender). The lubricated blend was compressed using 27 station compression machine (M/s. Cadmach Machinery India) with 12 mm round biconvex punches at a target weight of about 550mg or 600mg (as applicable) and with a hardness of 14-16 Kp. The formula compositions employed in the current study are compiled in Table 1 and process flow chart is depicted in Figure 1 below.

Table 1. Formulations of hydrogel matrix tablets using HPMC and different disintegrants

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation</th>
<th>Batch Number</th>
<th>F001</th>
<th>F002</th>
<th>F003</th>
<th>F004</th>
<th>F005</th>
<th>F006</th>
<th>F007</th>
<th>F008</th>
<th>F009</th>
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<tr>
<td>Propranolol HCl (mg)</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
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<tr>
<td>HPMC (K100M) (mg)</td>
<td>80</td>
<td>160</td>
<td>240</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>160</td>
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<td>160</td>
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<tr>
<td>CaCMC (mg)</td>
<td>--</td>
<td>-</td>
<td>160</td>
<td>--</td>
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<td>--</td>
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<tr>
<td>CP (mg)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>160</td>
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<tr>
<td>CCS (mg)</td>
<td>--</td>
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<td>--</td>
<td>160</td>
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<tr>
<td>SSG (mg)</td>
<td>--</td>
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<td>PVP-K30 (mg)</td>
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<td>IPA (mL)</td>
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<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
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<tr>
<td>DCP (mg)</td>
<td>245.8</td>
<td>165.8</td>
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<td>Aerosil (mg)</td>
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<td>Magnesium stearate (mg)</td>
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<td>5</td>
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<td>5</td>
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<td>5</td>
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<td>5</td>
</tr>
<tr>
<td>Tablet Weight (mg)</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
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<td>550</td>
<td>550</td>
<td>550</td>
<td>600</td>
<td>600</td>
</tr>
</tbody>
</table>

HPMC: Hydroxypropyl methylcellulose; CaCMC: Calcium carboxymethyl cellulose; CP: Crospovidone; CCS: Croscarmellose sodium; SSG: Sodium starch glycolate; PVP K-30: Povidone K-30; IPA: Isopropyl Alcohol; DCP: Dicalcium Phosphate; Aerosil: Colloidal silicon dioxide
Physicochemical evaluation
The compressed tablets of different formula compositions were evaluated for varied physicochemical parameters such as physical appearance, weight variation, thickness, hardness, friability, drug content and in-vitro drug release behavior.

Drug release studies
In-vitro drug release studies were performed using USP Type I (M/s. Lab India Disso 2000) apparatus at 100 rpm. Dissolution medium was 900 mL of pH 1.2 HCl (up to 1.5 h) followed by pH 6.8 phosphate buffer up to 24 h maintained at 37 ± 0.5°C. Aliquots of the samples were collected at specified intervals and analyzed by UV-Visible spectrophotometry (Shimadzu UV-2450) at λmax 290 nm. Dissolution was also performed in other media like 0.01N HCl (pH 1.2 for 24 h) and acetate buffer pH 4.5 (for 24 h) to study the effect of different pH conditions on drug release.

In-vitro drug release: data analysis
In order to have comparative conclusion for drug release profiles obtained from different formulations, the drug release data was analyzed through computation of various drug release parameters viz. time taken to release 50% of the drug (t50%), mean dissolution time (MDT) and percent dissolution efficiency at various time points (%DE).
The t50% values were computed from regression equation obtained from percent undissolved versus time curves, generated for respective formulations. The MDT values were obtained as per the following equation [16]:

Figure 1. Schematic flow of manufacturing process employed for preparation of HPMC-disintegrant hydrogel matrix tablets.
Various kinetic models were employed to describe the probable release kinetics displayed by HPMC matrices, prepared in combination with different disintegrants. These included Zero-order, First-order, Higuchi and Korsmeyer-Peppas kinetic models and are explained by following set of equations:

Zero-order rate equation (Equation 3), describes the systems where the drug release rate is independent of its initial amount [16,18].

\[
M_0 - M_t = k_0 t
\]

\( \ldots (3) \)

where, M0, Mt are drug amount taken at time equal to zero, and amount dissolved at specific time, t, respectively. The term k0 is zero order rate constant.

The first-order equation (Equation 4) describes the release from a system where release rate is amount dependent [19].

\[
\ln \left( \frac{M_0}{M_t} \right) = k_1 t
\]

\( \ldots (4) \)

Where, k1 is the first order rate constant.

Higuchi described the release of drugs from insoluble matrix as a square root of time (Equation 5) dependent process, based on Fickian diffusion [20].

\[
M_t = K \sqrt{t}
\]

\( \ldots (5) \)

Where, K is the constant reflecting the design variables of the system.

Korsmeyer derived a relationship (Equation 6) which described drug release from a polymeric system to find out the mechanism of drug release [21].

\[
\frac{M_t}{M_{\infty}} = k_t t^n
\]

\( \ldots (6) \)

Where, M is the drug amount released at infinite time and Mt /M is the fraction of drug released at time t, k is the rate constant and n is the release exponent that characterizes the mechanism of drug release.

Various drug release rates were computed as per the above described models and compared for the mechanism of drug release from the developed matrices.

### Swelling studies

The swelling behavior of the formulations containing polymer alone and combination of polymer with different disintegrants (i.e., F001-F007) was studied. Three tablets of each batch were kept in a beaker containing 100 mL distilled water at 37 ± 1°C. At selected time points, the tablets were withdrawn, wiped with tissue paper and weighed. The rate of uptake of water by the matrix system was calculated at predetermined intervals. The swelling index was calculated using the following equation [22]:

\[
\text{Water uptake} = \frac{W_t-W_0}{W_0} \times 100
\]

\( \ldots (7) \)

Where, W0 is initial weight of tablet, and Wt is the weight of the tablet at time t.

### Texture analysis

In addition to water uptake study, the swelling behavior of swollen matrices were further evaluated by textural analysis. The samples of different formulations (F001, F003, and F004-F007) were placed in dissolution vessels under conditions identical to those specified for dissolution studies. At the end of 24 h, the swollen matrices were patted lightly with tissue paper and subjected to textural profiling to obtain force-time profiles indicating work of probe penetration into the entire matrix. Textural analysis was performed using a TA.XT2i texture analyzer equipped with 50 kg load cell and Texture Expert software (Texture Technologies Corp. Scarsdale, NY/ Stable Micro Systems, Godalming, UK). The force-time profiles, associated with the penetration of a 3mm round-tipped steel probe into the swollen matrices, were monitored at a data acquisition rate of 200 points per second. The total work of penetration, which measures the gel strength in response to the resistance generated during probe displacement, was determined using equation 8.

\[
\text{Total work done through penetration} = W T = \int F dD
\]

\( \ldots (8) \)

Where, \( W \) = Work done; \( F \) = Force applied; \( d \) = Diameter of probe; \( D \) = Distance travelled.

### Stability study

Stability study was performed as per ICH guidelines on combination formulation of HPMC and CCS (F006) as it exhibited similar dissolution profile as that of marketed product which was considered as comparator, for evaluation in the current study. The
samples were stored in induction sealed HDPE (High Density Polyethylene) bottles at 40±2°C and 75±5% RH for a period of 3 months and analyzed for physical properties, drug content and drug release profile.

**Results**

**Physicochemical evaluation of HPMC-disintegrant matrix tablets**

The thickness of matrix tablets varied from 5.77 to 5.96 mm for F001-F007 and 6.24-6.28 mm for F008 and F009. The tablet weight was observed to be within acceptable limits. The hardness was observed within 14.75-15.86 Kp and friability was found to vary between 0.11% and 0.35%. The mean value of drug assay for all batches was observed to vary between 99.48 to 100.36%.

**Drug release profiles**

Figure 2a and 2b depict the drug release profiles of various formulations, manufactured employing either change in amount of polymers and/or disintegrants. For comparison, the drug release profile of the marketed long acting product of Propranolol Hydrochloride was also determined under identical dissolution conditions. Table 2 enlists various drug release parameters obtained for all formulations.

**Figure 2. Drug release profiles of developed HPMC-matrix formulations (a) with varying amount of drug:polymer ratio; (b) containing different types of disintegrants; (c) at different pH conditions**

**Table 2. Drug release parameters derived from drug release profiles for all HPMC-based formulations**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Formulation Batch Number</th>
<th>F001</th>
<th>F002</th>
<th>F003</th>
<th>F004</th>
<th>F005</th>
<th>F006</th>
<th>F007</th>
<th>F008</th>
<th>F009</th>
<th>Marketed product</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{50%}$ (h)</td>
<td></td>
<td>4.77</td>
<td>5.35</td>
<td>11.41</td>
<td>5.74</td>
<td>5.24</td>
<td>5.36</td>
<td>9.51</td>
<td>15.23</td>
<td>10.71</td>
<td>5.32</td>
</tr>
<tr>
<td>MDT (h)</td>
<td></td>
<td>4.69</td>
<td>4.86</td>
<td>7.39</td>
<td>5.71</td>
<td>5.75</td>
<td>5.90</td>
<td>8.67</td>
<td>5.86</td>
<td>7.42</td>
<td>5.03</td>
</tr>
<tr>
<td>DE4h (%)</td>
<td></td>
<td>36.6</td>
<td>30.9</td>
<td>18.7</td>
<td>30.1</td>
<td>35.4</td>
<td>28.8</td>
<td>21.6</td>
<td>19.2</td>
<td>19.3</td>
<td>23.9</td>
</tr>
<tr>
<td>DE14h (%)</td>
<td></td>
<td>62.1</td>
<td>56.3</td>
<td>35.6</td>
<td>55.9</td>
<td>58.7</td>
<td>56.7</td>
<td>42.4</td>
<td>35.8</td>
<td>37.7</td>
<td>56.6</td>
</tr>
<tr>
<td>DE24h (%)</td>
<td></td>
<td>72.2</td>
<td>67.2</td>
<td>47.9</td>
<td>71.0</td>
<td>71.3</td>
<td>70.3</td>
<td>59.3</td>
<td>45.8</td>
<td>50.8</td>
<td>70.1</td>
</tr>
</tbody>
</table>

%DE$_t$: percent dissolution efficiency at various time points, MDT: mean dissolution time and $t_{50\%}$: time taken to release 50% of the drug.

**Effect of polymer amount**

In order to study the effect of amount of polymer on drug release, the drug: polymer weight ratio was varied from 1:0.5 to 1:1.5 in batches F001-F003. Figure 2 (a) shows the effect of varying amount of HPMC on drug release, along with comparative release profile of marketed long acting product of Propranolol Hydrochloride. Table 2 reflects the 50% values for F001-F003 varying widely in the range of 4.77 to 11.41 h. Further, the parameters like MDT, DE4h (%), DE14h (%) and DE24h (%) also represent slowing of the drug release profile as the polymer amount is increased in the matrices.
Effect of disintegrants

Figure 2(b) portrays the drug release profiles obtained from formulations with different types of the disintegrant (F004-F009) along with the drug release profile of long acting marketed product. F004-F007 are the formulations encompassing varying type of disintegrant in the matrices with drug:polymer ratio as 1:0.5 and polymer:disintegrant ratio as 0.5:1. F008 and F009 formulations were prepared as combination matrices with higher amount of polymer (drug:polymer and polymer:disintegrant ratio as 1:0.1:0).

Effect of pH on disintegrant role on drug release

Figure 2c depicts drug release profiles of formulations F004-F007 in dissolution media with different pH conditions. The hydrogel matrices formulated in combination with CaCMC, CP and CCS showed similar drug release profiles across varied pH range. However, polymer-SSG combination matrices exhibited pH-dependent release with relatively faster drug release profiles in dissolution media like 0.01N HCl and acetate buffer (pH 4.5) when compared to dissolution medium with initial pH 1.2 (0.01 N HCl for 1.5 h) followed by pH 6.8 phosphate buffer up to 24 h.

Drug release kinetics

The regression parameters obtained after fitting the obtained data into various release kinetic models are summarized in Table 3. The goodness of fit for various investigated models ranked in the order of Higuchi > Korsmeyer-Peppas > First-order > Zero-order.

| Table 3. Statistical parameters of various formulations after fitting the data to various drug release kinetic models |
|---|---|---|---|---|---|---|---|---|---|
| HPMC (%) | Formulations | Disintegrant (%) | Zero order | First order | Higuchi | Korsmeyer-Peppas |
| Type | % w/w* | k0 | r² | k1 | r² | K | r² | n | r² |
| 15 | F001 | - | - | 10.5 | 0.7146 | -0.0609 | 0.8870 | 26.98 | 0.9847 | 0.3161 | 0.9728 |
| 30 | F002 | - | - | 9.3 | 0.7763 | -0.0525 | 0.9264 | 22.48 | 0.9816 | 0.3833 | 0.9669 |
| 44 | F003 | - | - | 4.4 | 0.7578 | -0.0253 | 0.8928 | 15.04 | 0.9934 | 0.4985 | 0.9944 |
| 15 | F004 | CaCMC | 29.09 | 8.7 | 0.7327 | -0.0572 | 0.9623 | 23.12 | 0.9904 | 0.4488 | 0.9765 |
| 15 | F005 | CP | 29.09 | 9.5 | 0.6124 | -0.0537 | 0.9645 | 23.59 | 0.9656 | 0.3407 | 0.9908 |
| 15 | F006 | CCS | 29.09 | 9.3 | 0.8601 | -0.0571 | 0.9940 | 22.87 | 0.9955 | 0.4420 | 0.9869 |
| 15 | F007 | SSG | 29.09 | 5.3 | 0.7933 | -0.0342 | 0.9444 | 17.28 | 0.9999 | 0.5411 | 0.9880 |
| 30 | F008 | CaCMC | 26.66 | 3.3 | 0.6672 | -0.0216 | 0.8922 | 14.03 | 0.9926 | 0.4461 | 0.9986 |
| 30 | F009 | SSG | 26.66 | 4.7 | 0.7903 | -0.0297 | 0.9799 | 15.92 | 0.9951 | 0.5151 | 0.9971 |
| Marketed product | - | - | 9.4 | 0.9569 | -0.0608 | 0.9941 | 22.96 | 0.9777 | 0.5781 | 0.9325 |

*with respect to total formula weight of the matrix tablet

CaCMC: Calcium carboxymethyl cellulose; CP: Crospovidone; CCS: Croscarmellose sodium; SSG: Sodium starch glycolate

Swelling studies

Figure 3 depicts the graph of swelling index for HPMC matrices versus time (up to 24 h) at different polymer amounts ranging from 15-45%w/w (i.e., F001-F003) as well as HPMC-disintegrant matrices (i.e., F004-F007). All formulations exhibited increase in swelling up till 7 h and thereafter decline in swelling indices were observed. As evident from graph, matrices with disintegrants exhibited higher swellability indices. Higher swelling indices were observed for SSG formulation (F007) than formulation with CCS (F006).

![Figure 3. Swelling Index of developed HPMC-matrices with different amounts of polymer and disintegrants](image-url)
Texture analysis

The total work of penetration, calculated as the area under the force–time curve indicates matrix stiffness or rigidity. For all the formulations (F001, F003, F004-F007), the work of penetration is graphically represented in Figure 4. It depicts the change in work of penetration versus time as the exposure to swelling medium is extended and hydration is increased. Figure 5 depicts the force-time curve for combination matrices after swelling at 24 h. The figure suggests lower force applied for the matrix formulated with CCS.

Figure 4. Comparative trend on work of penetration data obtained through texture analysis on swollen HPMC-disintegrant matrices

Stability studies

Figure 6 depicts the in-vitro drug release profile at initial time point and after 3 months. The % drug content was found to be 100.31% and 99.12% at initial and 3M time points during accelerated stability condition of 40°C ± 2°C/75% RH ± 5% RH.

Figure 6. In-vitro drug release profile of the Formulation F006 at initial and 3 months' time point
Discussion

The physicochemical parameters of the tablets viz. average weight, thickness, hardness, friability and assay were found to be within acceptable limits.

Drug release profile

The results of drug release profiles and the computed drug release parameters are discussed below:

Effect of polymer amount

Formulations with drug:polymer ratio as 1:0.5 and 1:1 (F001 and F002, respectively) exhibited initial burst release with incomplete release at 24 h, indicating initial fast release of the water-soluble drug followed by release retardation due to delayed swelling of the polymer (Figure 2a). More release retardation was observed with further increase in the polymer amount i.e., formulation with drug:polymer ratio as 1:1.5 (F003). The formulation F003 exhibited desired control of initial burst release due to increase in polymer amount, but, with incomplete extent of drug release in 24 h. The %DE values at various times also revealed that drug release from Formulation F001 (drug:polymer weight ratio 1:0.5) was quite faster than that of Formulation F002 and F003. When compared to marketed product for varied %DEt values, Formulation F002 exhibited faster initial release (%DE4h 30.9-23.9) but showed similarity in the later drug release profile. Formulation F003 however, exhibited retarded and incomplete drug release when compared to the marketed product (%DE4h, %DE14h, %DE24h of F003 less than those observed for marketed product). The observations indicated that release modification with polymer alone was inadequate; therefore, to ensure controlled and complete drug release, another release modifier was required to be coupled with the polymer, which could provide initial control but not hinder the extent of drug release with this polymer.

Effect of disintegrants

As per data indicated in Table 2 and drug release profiles shown in Figure 2a and 2b, all disintegrants except for CP, when coupled with polymer in the polymer:disintegrant ratio of 0.5:1 ratio, exhibited initial burst control as well as complete release in 24 h. In matrices with CP (F005), initial drug release was nearly similar to F001 (%DE4h values of F005 similar to that of F001). The enhanced control on initial drug release with other disintegrants (F004, F006 and F007) was however observed. It could be attributed to the rapid swelling of the disintegrant within the matrix, which block the pores and hinder the drug release. The drug release profiles of these combination matrices could provide complete release also, in contrast to F001 and F002 formulations. In the later phase of the dissolution, the gel matrices in all combination products (i.e., F004-F007) eventually eroded and led to nearly complete release of the drug. Values for parameters like t50%, %DE14h and %DE24h of formulations F004 to F007, when compared to that of formulation F001 indicate slight extension of the drug release profile in the combination matrices. Formulation with SSG (F007), exhibited relatively more control on initial burst release from matrix. This indicated synergizing effect of the swellable disintegrants for release retarding effect of HPMC. These parameters and profiles were observed to be comparable in magnitude to those of F002 formulation indicating that disintegrants in combination with lower amount of polymer could impart release modulation to the extent similar formulations containing higher amount of polymer alone but with added advantage of complete extent of drug release.

The study on effect of disintegrants CaCMC (F008) and SSG (F009) when coupled with higher amount of polymer (drug:polymer and polymer:disintegrant ratio as 1:1) revealed not only initial drug release control (%DE4h values as 19.2 for F008 and 19.3 for F009 vs. 30.9 for F002), but the extent was also observed to be retarded with corresponding %DE24h values as 45.8 for F008 and 50.8 for F009 versus 67.2 for F002. This indicated that disintegrants with higher polymer amount helped in controlling not only the initial burst but also synergized release retardation at later phase of dissolution and thereby resulting in incomplete release at 24 h. Therefore, the disintegrant should be paired with lower amount of HPMC only. The combination matrices formulated with polymer and CaCMC and CCS (F004, F006) exhibited similar drug release profile as that obtained with the marketed product.

Effect of pH on disintegrants role as release modulator

As evident from graph (Figure 2c), the formulations (F004-F006) with disintegrants CaCMC, Crospovidone and CCS provided pH independent control on initial and complete release in 24 h. However, formulation with SSG (F007) exhibited relatively faster initial release in dissolution media like 0.01N HCl and acetate buffer (pH 4.5) in comparison to that obtained in medium with 0.01N (pH 1.2 for 1.5 h) followed by pH 6.8 phosphate buffer thereafter. HPMC-disintegrant matrix prepared with SSG exhibited faster initial release which may be attributed to anionic nature of the disintegrant. Mixed reports are available on pH dependent disintegrant effect of CCS and SSG in literature [12, 23-25].

Drug release kinetics

High values for goodness of fit for Higuchi model reflected drug release mechanism to be primarily diffusion based. All models except for Zero-order were fitted considering the entire drug release profile i.e., up till 24 h. Since the extent of release varied at given time points, modeling analysis for zero-order was carried out by fitting the data up till about 70 % of the drug release. The drug release from all formulations was governed by Fickian diffusion except for formulation with higher polymer content (F003) and HPMC-SSG matrix formulations (F007 and F009). The latter formulations exhibited non-Fickian behavior, which showed a combination of diffusion as well as erosion mechanisms of drug release.
Swelling studies

Higher swelling propensity was observed with combination matrices (Figure 3). The swelling indices for each formulation were observed to increase till 7 h, which could be due to strong gelation of hydrogel tablets [26]. Tablet weights increased proportionally with rate of hydration over a period of time. Later on, they tended to decrease gradually due to erosion of outermost gelled layer of tablet into dissolution medium. These results were in consonance with earlier findings, which reported that disintegrants due to higher hydration rate and capillary action increased the penetration of water into the hydrophilic matrices leading to higher swelling index [12, 27]. Consequently, greater extents of swelling at a higher amount of polymers lead to increase in the tablet dimensions and increasing the diffusion pathways and thus decreasing the dissolution rates.

After peak hydration at 7 h, swollen matrices start to erode because inter-chain molecular forces of highly swollen polymers are not able to resist any external force. Upon erosion, the matrix system tends to breaks into smaller particles, leading to more drug release (26). The swelling index order of various disintegrants in combination matrices was observed to be SSG > CCS > CaCMC > CP. Higher swelling index were observed for SSG formulation (F007) than formulation with CCS (F006). However, the formulation with SSG was observed to have less physical integrity than F006. The Formulations F004 and F005 containing CaCMC and CP, respectively were observed to gelate slowly when compared to the formulations with other two disintegrants. This could be related to relatively faster initial drug release as well. However, these formulations were able to maintain the integrity of the hydrogel formed for the desired period of time unlike formulation with SSG (F007) thus rendering the extended and complete release of the drug.

Texture analysis

The combination hydrogels formulated with disintegrants (F004-F007) exhibited relatively higher value of work of penetration in comparison to hydrogels formulated without them (F001 and F003). This indicated relatively faster swelling in their presence leading to more gelation and consequently in higher work of penetration. The order for work of penetration of various disintegrants in combination matrices was observed to be SSG > CaCMC > CP > CCS (Figure 5). Due to presence of swellable polymers in the hydrogel matrices, the matrix system easily absorbed water and swelled significantly upon contact with water. Based on the type of swellable polymer and the amount used, the hydrogel formation and its dynamics vary [28]. The formation of hydrogel on the surface of matrix generally undergoes transition phases, from a glassy (dry) stage where the mobility of drug and the hydrophilic polymer is very low (owing to the solid compressed state), to a rubbery (wet) stage where the mobility of the polymer and drug substance is increased due to which drug diffusion takes place [29]. The formulations with no disintegrants showed that matrices exhibited lower work of penetration (Figure 4). In the formulations with disintegrants, the gelation occurred slowly and prolonged the drug release. Figure 4 showed that for all HPMC-disintegrant combination matrix formulations, work of penetration values were high at the initial time point and as the gelation of the hydrogel matrix progressed, the work of penetration values decreased and were low at 24 h as the hydrogel completely relaxed. Unlike swelling studies, F004 was however observed to exhibit work of penetration values comparable to other swellable disintegrants like CCS and SSG. Overall during swelling studies, the matrix swelling was observed to increase uptill 7 h. Such trend was however not observed in the textural analysis. This indicated that as the time lapsed, the swollen matrices simultaneously started eroding in turn losing the gel strength. This could have facilitated the complete release of drug over the studied time period of 24 h. Amongst all formulations, F006 containing CCS was observed to have least work of penetration value at the end of 24 h thus showing the complete relaxation of the hydrogel system and complete release of the water soluble drug from the developed matrix system (Figure 5).

Stability studies

Based on similarity in release profile, swelling studies and textural analysis, formulation F004 and F006 seemed to be promising combinations to achieve desired drug release profile. Stability study data for formulation F006, is presented here. No significant changes in physicochemical parameters and in-vitro drug release were observed in formulation F006, after 3 months of storage at 40±2°C &75±5% RH, indicating adequate drug product stability in the studied packaging configuration.

Conclusions

In the current work, the potential role of different disintegrants on release modulation of water soluble drug from HPMC matrix was investigated. The results have suggested that higher viscosity grade hydrophilic polymer alone was inadequate in providing the complete drug release along with control over initial rate. Combination of Polymer-disintegrant however, was able to provide complete drug release with varying degree of control over initial burst release. The drug release rates correlated with swelling properties of the matrices wherein disintegrant also played a key role. Overall, drug release was Fickian diffusion based except for SSG formulations where non-Fickian behavior was observed. Except for SSG based HPMC matrix, all polymer-disintegrant combinations showed pH-independent release. Texture analysis studies revealed the minimum work of penetration at 24 h for CCS formulation followed by other three formulations in the order of CP<CaCMC<SSG. High swelling indices associated with CCS formulation coupled with lower penetration work values indicated the drug release by both diffusion as well as polymer relaxation. Formulation with HPMC-CCS combination provided similar drug release to that of marketed product, and also showed good stability.
over accelerated 3 months stability study. The findings of
the current study suggest that polymer-disintegrant combina
tions can be successfully exploited to control or modulate the
drug release from the HPMC matrices of other highly water soluble drugs as well.

Authors’ Contributions
Sanjay Wagh has carried out the research work and compiled the
study findings. This research work has been carried out under the
supervision of Jayanthi Kumar. Both the authors have read and
approved the final manuscript.

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