Development and Evaluation of Ibuprofen Pellets Based on Sodium Alginate and Hydroxy Propyl Methyl Cellulose Blends
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ABSTRACT
Pellets which are agglomerates of fine powders or granules of drugs with spherical or semi-spherical shape, generally aimed for oral use, range from about 0.5 mm to 1.5 mm. The study was performed to microencapsulate Ibuprofen, which is a non-steroidal anti-inflammatory drugs (NSAIDs) through extrusion technique with the aid of sodium alginate and HPMC K100 LV in different proportions. After formulation physicochemical parameters like mean particle size, contraction ratio, surface morphology, moisture content, buoyancy test, swelling index, angle of repose, percent yield, drug entrapment efficiency and drug release potential of the formulated preparation were investigated. From results, it is clear that with the increasing sodium alginate concentration, mean particle size enhances and a poor size distribution in the range of 1.258 mm to 1.783 mm existed among the batches and similar characteristics also appeared for angle of repose and swelling index. In contrary, relationship between contraction ratio, percent yield, drug content, concentration on loose surface, and drug entrapment efficiency value with sodium alginate concentration is erratic rather than linear and formulated microspheres floated in the simulated gastric fluid, water, 0.9 % NaCl solution. Scanning electron microscopy (SEM) provides information about the surface morphology and drug distribution on the surface. The formulated pellets showed drug release in the range of 8.67 – 35.4 % mg/hr and release kinetics shows maximum resemblance with Higuchi model. Finally, through the overview of the physiochemical parameters performed on the current study sable Ibuprofen pellets could be synthesized.

KEYWORDS
Pellets, NSAIDs, Extrusion, Surface Morphology, Drug Entrapment Efficiency

INTRODUCTION
In order to ensure the efficiency of a drug therapy, optimum concentration should be remained in the aimed tissue or blood system for expected period.

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Recently, the development of new drug delivery system is of great concern, compared to the innovation of nascent drug entity due to enormous expenditure on the development process. Criteria such as safety and efficacy as well as improved patient compliance is the principle target of sustain drug delivery system. As these dosage form can hold the drug
concentration between the minimum effective concentration and minimum toxic concentration for a prolong period of time, their subsequent application is rising in instances like acute and chronic diseases and hence minimize side effects with frequency of dosing accounted a twofold or grater reduction, in contrast to conventional dosage form.\textsuperscript{1}

Today, microsphere is experiencing a greater attention as an effective means of sustain drug delivery system as some beneficial effects like decreased dosage and systemic side effects, lowered in medication frequency and enhancement of patient compliance are evident. Moreover, microspheres prepared from biodegradable and biocompatible polymer are concerning for sustained drug delivery system and some of these polymers are employed as a controlled drugs release carriers with their approved use by the US Food and Drug Administration (FDA) for surgical sutures, implantable devices.\textsuperscript{2}

A polysaccharide, sodium alginate, composed of α-L-guluronic acid (G) and β-D-mannuronic acid (M), is used for making gel beads in presence of its high viscosity solution and divalent cation such as Ca\textsuperscript{2+}.\textsuperscript{3} In addition, due to the biodegradability and biocompatibility as well as non-toxic nature, alginates are of potential pharmaceutical interest, making alginate hydrogels which poses potential to be used as either controlled release membrane or matrix, suitable for sustain drug delivery system.\textsuperscript{4} Moreover, the effects of sodium alginate beads to evaluate the gastroretentive properties in order to maximize control over drug release or to achieve a site-specific delivery with the effect of changing dosage levels have been examined.\textsuperscript{5}

The objective of the present study was to formulate calcium-induced alginate pellets containing ibuprofen as a multi-particulate system by extrusion / spherization as this technique allows the preparation of spherical pellets with regular shapes and sizes, smooth surface characteristics which are suitable for employing of a release retarding membrane.\textsuperscript{4}

### MATERIALS AND METHOD

#### Materials

Ibuprofen was a gift sample from Globe Pharmaceuticals Ltd., Bangladesh. Sodium alginate was purchased from LOBA Chemicals Pvt Ltd., India and Calcium chloride from Merk, India. HPMC (Methocel K100 LV CR Premium USP) were bought from Aircon Asia Pvt Ltd. India. All other reagents and solvents used were of analytical grade satisfying pharmacopoeial specifications were commercially available.

#### Methods

**Pellets Preparation by Extrusion/Spheronization**

At first, Sodium Alginate (1%, 1.5 %, 2% w/v) was soaked in 150 ml distilled water for overnight to prepare gel after homogenization through electronic stirring (4000rpm) for half an hour. Then allocated amount of HPMC K100LV for each batch were added to the gel and further stirred for thirty minutes. After that, Ibuprofen (1 gm) was added to the resulting mixture, followed by homogenized for another 30 minutes. Mixture formed through the above procedure was applied drop wise with the aid of a needle attached to a 5ml syringe into 200ml of calcium chloride solution (1% w/v), set above the magnetic stirrer. The droplets then turned into distinct matrices upon contact with calcium chloride solution on which the drug loaded pellets were stirred for 15 minutes, prior to isolation through cotton. Lastly, the separated pellets were washed with 200 ml distilled water and dried in the room temperature for approximately 12 hours.\textsuperscript{4}

**Study of Particle Size and Contraction Ratio of Ibuprofen Pellet**

At first, the particle sizes (n=20) were determined with a digital slide calipers (Fisher Brand) and then Scanning Electron Microscopy were used. Pellets contraction ratio was computed by dividing the mean volume of dried gel (dried pellet) by that of the hydrogel (wet pellet).\textsuperscript{5}
Surface Morphology Study
Morphology study of Ibuprofen pellets were performed through Scanning Electron Microscopy (SEM) (Hitachi, S-3400N) at the Bangladesh Center of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh.

Buoyancy of the Preparations
To examine the floating status of the pellets, ten beads from each were placed in 50 ml of individual test solution and upon floated on the solution, pellets were considered to be buoyant.

Swelling Study
Percentage of weight gain by the beads was measured to evaluate the extent of swelling. At first, 10 mg Ibuprofen beads from each batch namely F1, F2, F3, F4, F5, F6 were soaked in pH 1.2 chloride buffers in Petri dishes for two hours and then removed followed by diffuse in tissue paper to remove water and weighed. Percent weight gained by the beads was calculated by the following formula.

Swelling ratio = \( \frac{(M_t - M_0)}{M_0} \times 100 \)

Where,
- \( M_t \) = weight of beads at time ‘t’ and
- \( M_0 \) = weight of beads at time, \( t = 0 \).

Angle of Repose
Angle of repose was determined by a fixed funnel method, is necessary in case of knowing the flowability of pellets. The angle of repose (\( \theta \)) for samples were calculated using the formula:

\[ \text{Angle of repose} = \tan^{-1}\left(\frac{h}{r}\right) \]

Where, \( r \) is the radius of pile and \( h \) is the height of the pile.

Determination of Percentage Yield and Drug Entrapment Efficiency
It ensures the efficiency and importance of the employed procedure in the pelletization technique during which process parameter and amount of active ingredient and polymers are determinant factors for the product yield.

Percentage of yield can be calculated by the following formula:

\[ \% \text{ yield} = \frac{\text{wt of pellets}}{\text{wt of drug + wt of polymers}} \times 100 \]

By using the following formula Drug Entrapment Efficiency (DEE) was calculated:

\[ \% \text{ DEE} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \]

Loose Surface Crystal Study (LSC)
At first, 200 mg of pellets was dispersed in 100 ml of phosphate buffer (pH 7.4) followed by stirred in a mechanical shaker for 15 minutes and later analyzed spectrophotometrically at 265 nm.

Drug Content
UV/Visible spectrophotometric method was employed to measure the drug content of Ibuprofen pellets and for this purpose at first, pellets were crushed to fine powder, from which 100 mg equivalent of Ibuprofen were shifted to 100 ml volumetric flask followed by diluted with 100 ml methanol. Then, to ensure the complete extraction of the drug from the pellets, the mixture was kept on a rotary shaker for 60 minutes. Later, 1 ml of the solution was collected after filtration and further diluted with 100 ml methanol. Then absorbance was taken at 265 nm and with the help of calibration curve drug content was estimated.

In-Vitro Dissolution of Pellet
Dissolution test were performed by USP apparatus 2 (rotating paddle method) with 10 mg equivalent Ibuprofen pellets in 900 ml of dissolution medium maintained at 37±0.5°C and rotation speed was 50 rpm. Dissolution medium was pH 3 chloride buffers from which 10 ml was withdrawn at predetermined rate intervals of 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 105 min, and 120 min and replaced with an equal volume of medium in order to maintain the volume constant. Then, the absorbance was taken at 265 nm in UV spectrophotometer to measure the amount of drug release.
Determination of Drug Release Kinetics

To understand the release mechanism with the help of correlation co-efficient and p value for Higuchi, Zero order and first order model, statistical software (SPSS 16) were used. The correlation coefficients with better statistical fit were used as the main criteria and hence equation with maximum correlation coefficient was considered to be the most suitable model for each system.10

RESULTS AND DISCUSSION

Evaluation of Pellet Preparation Method

During extrusion / spheranization technique, homogeneity of the wet mass and non-adherence of the extrudates throughout extrusion, is preferable and hence proper formulation of the wet mass to achieve a plastic cohesive mass is necessary. Beside this, extrudates should possess adequate mechanical properties and brittle behavior to formulate discrete particles instead of large amount of fine particles.9

Table 1: Formulations of pellets

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Sodium Alginate</th>
<th>HPMC K100LV</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent used</td>
<td>Amt. (gm)</td>
<td>Amt. (gm)</td>
</tr>
<tr>
<td>F 1</td>
<td>1</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>F 2</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>F 3</td>
<td>1.5</td>
<td>2.25</td>
<td>0.5</td>
</tr>
<tr>
<td>F 4</td>
<td>1.5</td>
<td>2.25</td>
<td>1</td>
</tr>
<tr>
<td>F 5</td>
<td>2</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>F 6</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

In the present study, Na-alginate and HPMC were used as polymer and with changes in polymer concentration none of the batches create any problem throughout extrusion, in contrary showed enough extrudability properties. Use of extrusion / spheranization technique to prepare pellets with the aid of Na-alginate and HPMC as polymer and binder was reported in earlier studies.5,9 Since a chelate structure, egg box junction between alginate and calcium ions, was formed Ibuprofen was trapped in sodium alginate beads.11 The composition of all formulations are described in table 1.

Particle Size and Contraction Ratio of Ibuprofen Pellets

Table 2 represents the diameter and contraction ratio of Ibuprofen pellets. To achieve smaller size distribution in the formulated pellets it is ideal to employ optimal formulation and processing conditions. Mean particle size of the formulated batches (F 1 – F 6) were found in the limit of 1.258 ± 0.105 to 1.783 ± 0.115 which revealed a narrower size distribution of pellets with insignificant variation in spite of varying concentration and amount of Na-alginate and HPMC. Amount of Na-alginate and HPMC differ in each batch and as HPMC has adhesive and binder property, it made the formulation denser, aid in the formulation of larger particles. Effect of increasing amount of HPMC K4M, HPMC K100LV, HPMC 6 cp in elevating size distribution was proposed in earlier studies.9 Contraction ratio which ranges from 0.095 to 0.296, as like as the particle diameter was also found in a small scale. In an earlier study5, influence of Na-alginate on contraction ratio was reported as unworthy of notice.

Scanning Electron Microscopy of Bromhexine Pellets

Back-scattered electron imaging differs from secondary electron imaging and employs high-energy flexible electrons to observe atomic number differences. Higher atomic number elements reflect or highly deflect more electrons unlike lower atomic number elements which absorb electrons along the primary electron axis and darkness appeared on SEM photographs. For elements C, N and Ca, the order of brightness on the micrographs is C < N < Ca.4
Ibuprofen pellets were subjected to scanning electron microscopy (HITACHI, Model: S-3400N) magnification range 10-3500 to analyze pellet morphology, size distribution and surface structure. SEM micrographs show the diameter of pellets from 1.17 to 1.54 mm (Figure 1) with rough surface and as well as a sandy appearance (Figure 2) due to the association of drug crystals on the outer surface of the microspheres is also observed (Figure 3). Associated drug crystals on the surface probably the result of drug migration with water during drying, similar effects were also observed in earlier studies. SEM photograph also shows the dispersion of drug in Ibuprofen loaded Alg -Ca based pellets.

**Buoyancy of Pellets**

Formulated pellets of all the batches, floats in water, 0.9 % NaCl and simulated GI fluid upon infusing in these solutions. Similar consequence was reported in earlier studies for drug ladened Alginate-Calcium beads.

**Swelling Behavior**

Effect of swelling study is demonstrated in table 2. Swelling index value rises with increasing sodium alginate concentration, yet with the increasing rate of hydration, weight gain with higher swelling index is depicted in case of all batches. Slower erosion of the outer layer in chloride buffer is also ascribable towards higher value of swelling index. Report on increasing swelling index with increasing rate of hydration up to 3 hours was documented in previous study.

**Angle of Repose**

Value for the angle of repose is presented in table 2 and reveals that the formulated pellets have good flow property. The values are within the limit of 13.49 to 25.72 and with the increase of sodium alginate and HPMC concentration, values have risen upward.

**Percent Yield and Drug Entrapment Efficiency**

Losses of final product during extrusion/spheronization were occurred due to
the mechanical variables and thus impede 100% yield. All the formulated batches exhibit better percent yield, ranges from 85.71 – 95.67 % (Table 2), not significantly affected with the variation of sodium alginate and HPMC concentration.

Microsphere of all the batches showed good encapsulation efficiency and was in the range of 47.38 to 94.4 % (Table 2), minimum for batch F 4 (47.38 %) and maximum for F 1 (94.4%). It is clear from the table that, increasing concentration of sodium alginate yields bigger spheres and hence greater amount of drug could be entrapped (except in batch F 4). This may be due to greater accessibility of active calcium binding site and subsequent higher intensity of cross linking with increasing sodium alginate concentration which in addition, form dense matrix structure and results in the reduced loss of drug in the curing medium. Increase of drug entrapment with increasing sodium alginate for spheronized pellets has been reported in earlier studies.\textsuperscript{12}

**Loose Surface Crystal**

This parameter helps to measure the amount of drug remain un-entrapped on pellets surface and data are presented on table 2. Concentration of free drug on the pellets surface reduced with increasing concentration of sodium alginate and HPMC in earlier studies.\textsuperscript{12} Concentration of free drug on the pellets surface reduced with increasing concentration of sodium alginate leads to greater entrapment of drug in the dense matrix structure and similar effect was observed in earlier studies.\textsuperscript{12}

**Drug Content**

Formulation of all the batches exhibits the presence of a satisfactory amount of drug in the pellets and ranges between 80.12 % to 92.78 % (Table 2).

**Drug Release from Ibuprofen Pellets**

Value of correlation coefficients and drug release rate (mg/hr) from pellets are present in table 3 and figure 4 which is prepared by plotting amount of drug release per hour (mg/hr) against batches depicts drug release profile.

Release rate from the formulated Ibuprofen pellets is moderate and decreased with increasing sodium alginate and HPMC concentration, although differ in batch F3 and F4. Data from the report executed earlier\textsuperscript{10,13,14}, also evident the effect of HPMC and sodium alginate in delaying drug release from pellets. Batches F1 to F6 with correlation coefficient values 0.871 to 0.303 are in highest linearity with Higuchi model, applicable for release of drug through the process of diffusion through water filled pores in the matrix.

### Table 2: Physical Properties of Ibuprofen Pellets

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Diameter of Dried pellets\textsuperscript{a}</th>
<th>Contraction ratio (CR)</th>
<th>Swelling index (%)(at 2 hours)</th>
<th>Angle of Repose</th>
<th>Percent yield</th>
<th>Percent Drug Content</th>
<th>Concentration on loose surface</th>
<th>Percent of DEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1</td>
<td>1.258 ± 0.105</td>
<td>0.136</td>
<td>23.74</td>
<td>13.49</td>
<td>95.23</td>
<td>85.34</td>
<td>1.227</td>
<td>94.4</td>
</tr>
<tr>
<td>F 2</td>
<td>1.152 ± 0.251</td>
<td>0.095</td>
<td>27.68</td>
<td>14.56</td>
<td>85.71</td>
<td>80.12</td>
<td>0.270</td>
<td>69.74</td>
</tr>
<tr>
<td>F 3</td>
<td>1.357 ± 0.189</td>
<td>0.145</td>
<td>31.74</td>
<td>19.29</td>
<td>90.67</td>
<td>87.45</td>
<td>0.564</td>
<td>64.53</td>
</tr>
<tr>
<td>F 4</td>
<td>1.304 ± 0.062</td>
<td>0.104</td>
<td>33.67</td>
<td>21.61</td>
<td>92.53</td>
<td>92.78</td>
<td>0.399</td>
<td>47.38</td>
</tr>
<tr>
<td>F 5</td>
<td>1.505 ± 0.231</td>
<td>0.194</td>
<td>35.17</td>
<td>22.38</td>
<td>91.36</td>
<td>90.65</td>
<td>0.182</td>
<td>59.17</td>
</tr>
<tr>
<td>F 6</td>
<td>1.783 ± 0.115</td>
<td>0.296</td>
<td>38.22</td>
<td>25.72</td>
<td>95.67</td>
<td>91.63</td>
<td>0.186</td>
<td>56.26</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The data are presented as mean value ± SD (n=20)
Ibuprofen, which is a very popular NSAID, was subjected to extrusion / spheronization technique to prepare pellets with the aid of polymers Sodium alginate and hydroxy propyl methyl cellulose (HPMC) K100LV. Then the physical properties of the formulated pellets were examined and a good correlation among the pellets particle size and contraction ratio with polymers concentrations were revealed. Scanning Electron Microscopy (SEM) were utilized to study the surface morphology and dissolution study was conducted by USP dissolution tester (Apparatus-II) followed by release pattern which were explained by different kinetic models, showed maximum conformity with Higuchi model. The above results gives light on the probability of successful formulation and human study could be conducted.

ACKNOWLEDGEMENT

The authors are very grateful to Globe Pharmaceuticals Ltd., Bangladesh because of providing Ibuprofen.

REFERENCES


<table>
<thead>
<tr>
<th>Batch No</th>
<th>Release Rate (%mg/hr)</th>
<th>r² of Higuchi Plot</th>
<th>r² of first order plot</th>
<th>r² of zero order plot</th>
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<tr>
<td>F 1</td>
<td>35.4</td>
<td>0.871</td>
<td>-0.714</td>
<td>0.692</td>
</tr>
<tr>
<td>F 2</td>
<td>9.6</td>
<td>0.771</td>
<td>0.104</td>
<td>0.552</td>
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<tr>
<td>F 3</td>
<td>16.2</td>
<td>0.832</td>
<td>-0.693</td>
<td>0.688</td>
</tr>
<tr>
<td>F 4</td>
<td>30</td>
<td>0.720</td>
<td>-0.449</td>
<td>0.579</td>
</tr>
<tr>
<td>F 5</td>
<td>10.8</td>
<td>0.724</td>
<td>-0.567</td>
<td>0.574</td>
</tr>
<tr>
<td>F 6</td>
<td>8.67</td>
<td>0.303</td>
<td>-0.134</td>
<td>0.156</td>
</tr>
</tbody>
</table>

Table 3: *In vitro* drug release profile

Figure 4: Drug release rate

CONCLUSION


