Design and Characterization of Enteric Coated Pellets of Aspirin Using Hot-Melt Coating Technique

*S. G. Sudke1, D. M. Sakarakar2

1. SGSPS Institute of Pharmacy, Kaulkhed, Akola, Dist: Akola (MS), India.
2. Sudhakarrao Naik Institute of Pharmacy, Pusad, Dist: Yavatmal (MS), India.

ABSTRACT
Generally enteric coating is organic solvent based dispersion or solution of polymer which is equally hazardous to the environment and operators. Hot-melt coating (HMC) devoid the use of solvents and hence it is cheap, environment friendly, safe and rapid process. The objective of present study was to ensure the suitability of HMC as an enteric coating technique. Aspirin was used as model drug due to its stomach mucosal irritation and ulcerogenic property. Pellets of aspirin prepared by extrusion-spheronization technique were used as coating substrate. Stearic acid (SA) and palmitic acid (PA) were evaluated as enteric HMC materials. HMC was carried out in a specially modified coating pan and by applying SA and PA in molten state onto preheated pellets to achieve a coating level of 5-10% w/w. Hot-melt coated pellets were evaluated for disintegration pH and in vitro dissolution in the pH range 1.2 to 6.8, along with basic micromeritics. Scanning electron microscopy (SEM) of coated pellets showed a uniform and smooth coating. These results indicated that HMC of both SA and PA exhibited very good enteric coating ability. The coated pellets showed negligible drug release in acidic pH. As the pellets were subsequently transferred to a higher pH level, a gradual increase in release of the drug from the pellets was observed with increasing pH of the dissolution media. The release was dependent upon coating extent, providing sustained enteric release as opposed to abrupt release with mixed release kinetics.

Keywords: Aspirin, enteric coating, extrusion-spheronization, hot-melt coating, palmitic acid, stearic acid.

Received 23 Feb 2013 Received in revised form 06 March 2013 Accepted 11 March 2013

*Address for correspondence:
Prof. Suresh G. Sudke
SGSPS Institute of Pharmacy, Kaulkhed, Akola, Dist: Akola (MS), India.
E-mail: sureshsudke@gmail.com

INTRODUCTION
Enteric coated dosage forms are designed to resist the acidic environment of the stomach and disintegrate in the higher pH environment of the intestinal fluid. The main reasons for using an enteric coating is to protect the stomach wall from the harmful effect of the drug in a dosage form (NSAIDs like diclofenac, ibuprofen and naproxen) [1], to prevent degradation of the drug by gastric contents (erythromycin, insulin, pancreatin, penicillin) [2], to release the drugs with site-specific absorption in the intestine, to deliver the drugs intended for local action in intestine (intestinal antisepsics) and to provide a lag time of between 3 and 4 hr and to bypass systemic absorption of drugs [3]. An enteric coating protects the drug during transit through the acidic medium of the stomach. Upon entering the higher pH environment of the duodenum, the coating is dissolved and the drug becomes available for absorption. Such a coating also provides protection for the gut mucosa when the drug is capable of producing gastric distress or nausea due to irritation. Enteric coating can also be used to deliver the active ingredients that are optimally absorbed from a particular region of the intestine like to the upper part of the small intestine, so as to enhance the bioavailability of the drugs.

The materials used for enteric coating are either water resistant or pH sensitive. Water resistant materials are digested or emulsified by intestinal juices whereas pH-
sensitive materials slowly swell and burst when solvated. These materials can be applied to solid dosage forms (capsules, granules, pellets, or tablets) from aqueous latex or pseudo-latex, dispersions, aqueous solutions of alkali salts or organic solvent solutions. Enteric-coated systems utilize polymeric coatings that are insoluble in the gastric media and therefore prevent or retard drug release in the stomach.

Various types of pH sensitive (ionizable) polymers are commercially available. The most commonly used pH-sensitive enteric polymers available today includes cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP), and methacrylic acid (Eudragit) copolymers. These polymers dissolve at various pH levels ranging between 4.8 and 7.2 [3]. The limitations of enteric coated dosage forms include the possibility of duodenal irritation from caustic drugs and an increase in inter-subject variability due to the presentation to the small intestine of a dosage form that needs to undergo disintegration and dissolution versus a disintegrated and partially dissolved drug substance.

A common problem associated with water resistant polymer is that, to provide an enteric effect, the film might be so thick that if the dosage form travels too fast through the gastrointestinal tract, solubilization in the intestinal fluid may never be achieved. With many aqueous enteric coating formulations the risk is of premature drug permeation through the enteric coat into the stomach. This can be due to increased permeability of the aqueous film coating or to high water solubility of the drug [4, 5]. If the active ingredients are freely water soluble, they may dissolve in the spray mist during the coating process, resulting in active ingredients being included in the film. Organic solvent-based systems have some disadvantages with respect to ecological, toxicological and manufacturing safety concerns. Enteric coating has been employed for the number of drugs, including ammonium chloride, aspirin, diethylstilbestrol, divalproex, erythromycin and potassium chloride.

Hot-melt coating agents are the materials that undergo a transition from solid or semi-solid state at lower temperature, to liquid or semi-liquid state at higher temperature [6]. Receiving much attention recently, HMC systems have become an immerging area in the pharmaceutical industry and concerted effort has been made to develop alternatives to organic and aqueous polymer system [7]. There are various HMC techniques which includes melt coating, hot-melt spray coating, solid dispersion hot-melt coating, hot-melt direct blending coating, melt granulation, melt extrusion, melt dispersion and pastillation [8-10]. Development of novel lipophilic excipients has provided impetus to research in the area of processing techniques involving molten states [11]. HMC methods have various advantages over conventional polymer coatings. The coating material can be applied without organic solvents at high application rate. Therefore shorter processing time is required for HMC. These coatings can be applied onto solid dosage forms in the form of hot melts, hot emulsions or suspensions (colloidal particles). In basic HMC, the coating material is applied onto the substrate surface in the hot-melt state.

The objective of the present study was to evaluate effectiveness of HMC technique as a method to obtain enteric coating. Pellets were used as multiple unit system in present study because they are equally distributed throughout the gastrointestinal tract and the gastrointestinal transit time of such systems are more reproducible and repeatable than those of single-unit tablets or capsules [12, 13]. Aspirin was selected as the model drug because it has a tendency for causing gastric irritation and even ulceration in some cases and is an ideal drug candidate for enteric coating. Stearic acid (SA) and palmitic acid (PA) were selected as the hot-melt enteric coating materials.

**MATERIALS AND METHODS**

**Materials:** Aspirin was received as a gift sample from Usan Pharma Pvt. Ltd., (Badodara, India). Stearic acid and palmitic acid were purchased from S. D. Fine Chemicals, (Mumbai, India). Microcrystalline cellulose (Avicel PH 101), lactose monohydrate and povidone (K-30) were generously gifted by FMC biopolymer
The composition of various formulations is given in [Table 1]. Pellets of aspirin with microcrystalline cellulose (MCC)-lactose monohydrate were prepared by extrusion-spheronization method using 5 % povidone (K-30) as a binder solution prepared in isopropyl alcohol. A damp mass was prepared by mixing aspirin, MCC, lactose and granulating this with binder solution. The damp mass was then extruded through a die-roller extruder. Extrudes were spheronized with a 1.2 mm cross hatch plate at 900 rpm for 5 min. The pellets were dried at 60°C for 2 hr in a hot air oven.

### Table 1: Formulation of SA and PA coated pellets of aspirin.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pellet Composition</strong></td>
<td>F1</td>
</tr>
<tr>
<td>Aspirin#</td>
<td>20</td>
</tr>
<tr>
<td>MCC (Avicel PH 101)#</td>
<td>50</td>
</tr>
<tr>
<td>Lactose#</td>
<td>27</td>
</tr>
<tr>
<td>Povidone (K-30)#</td>
<td>3</td>
</tr>
<tr>
<td><strong>Coating Composition</strong></td>
<td></td>
</tr>
<tr>
<td>Stearic acid (SA)#</td>
<td>5</td>
</tr>
<tr>
<td>Palmitic acid (PA) #</td>
<td>-</td>
</tr>
</tbody>
</table>

# indicates all weight were in mg.

1.2 **Hot-melt coating of pellets:** Accurately weighed SA and PA were melted in separate containers. Pre-weighed and pre-heated drug pellets were placed into the modified coating pan with four radially arranged baffles without spray system and allowed to attain a temperature of about 50°C. The molten wax was poured slowly and uniformly over tumbling pellets with constant rotation at 25 rpm of the coating pan. The coating level was determined by frequently taking weight readings of the coated pellets until the desired coating level was achieved. Finally, the hot-melt coated pellets were cured at 30°C for 24 hr.

2 **Evaluation of Hot-Melt Coated Pellets:**

2.1 **Size Distribution:** The size distribution was determined using a sieve shaker and set of 4 ASTM sieves (#10, #14, #20, and #30) for 5 min. The size distribution expresses the efficiency of the process to manufacture uniform size pellets.

2.2 **Hardness and friability of the pellet:** The hardness of hot-melt coated pellets was examined by a Veego digital dial type hardness tester (Veego Scientific®, India). For the friability study, 10 g pre-weighed sample was collected on a sieve having 0.85 mm apertures with 25 glass beads (3 mm in diameter) were placed in a Roche friabilator (Veego Scientific®, India) and operated for 100 revolutions at a speed of 25 rpm. The mass of pellets was collected again on a sieve with 0.85 mm apertures. The smaller particles were allowed to pass through the sieve and pellets reweighed. Friability was determined as the percentage loss of mass of the pellets post test [15].

2.3 **Determination of bulk and tapped density:** For measuring bulk density, 25 g of pellets of 14/20 mesh fraction were poured gently through a glass funnel into a
100 ml calibrated measuring cylinder. The surface was carefully made smooth with 3 tapping. The bulk density was then calculated by dividing weight by volume. The tapped density was also measured in a similar fashion as bulk density but the final volume was measured after tapping the cylinder from the height of 3 inches until a constant volume was obtained using tap density apparatus (Electrolab®, India). Compressibility index and Hausner ratio were determined from bulk density and tapped density values for respective pellet formulations.

2.4 Determination of drug content: The drug content in each pellet formulation was determined by weighing crushed sample equivalent to 50.0 mg of aspirin and dissolved in 50 ml methanol. The sample solution was diluted with 6.8 pH phosphate buffer and sonicated for 20 min (PCI®, India). The sample solution was centrifuged and filtered through 0.45 µm membrane filter. A 5.0 ml volume of this solution was diluted suitably and absorbance measured at 265.0 nm using a UV-Visible spectrophotometer (Shimadzu®, UV-1601, Japan).

2.5 Scanning electron microscopy: The coated pellets were sputtered with gold for 5 min using a sputter coater (Auto Fine Coater, Jeol®, JFC-1300, Japan). The microphotographs were observed at 30X and 500X magnifications. The surface of pellets was examined by scanning electron microscopy (SEM, Jeol® JSM 5600 LV, Jeol, Japan) at 10 kV.

2.6 Determination of disintegration pH of pellets [16]: Release rate of aspirin from uncoated and coated pellets was studied as a function of gradual increase in pH of the dissolution medium. The test was carried out on a USP XXIV type I dissolution test apparatus (Electrolab®, India). Initially, accurately weighed amount the pellets were placed in a basket. A 500 ml volume of 0.1N hydrochloric acid (pH 1.2) was taken as the dissolution medium and stirred at 50 rpm. After an initial period of 15 min, the pH was gradually increased every 10 min by addition of 0.4 M disodium hydrogen phosphate. Drug concentrations prior to each addition of disodium hydrogen phosphate were measured spectrophotometrically after alkalization by 1N sodium hydroxide at 265.0 nm. Maximum dissolution rate of the model drug was considered indicative of the pH value at which pellet disintegration had occurred. This test provides some notion of the suitability of these materials as enteric coating materials [17].

2.7 Drug release study: In vitro drug release from hot-melt enteric coated pellets was assessed using dissolution a testing apparatus USP XXIV type I (Electrolab®, India) at 100 rpm in 900 ml of 0.1N hydrochloric acid for the first 2 hr followed by pH 6.8 phosphate buffer. The percentage drug released from the pellets was determined using UV-Visible spectrophotometrically with reference to a linear calibration curve at a wavelength of 265.0 nm. The drug release data was computed in light of different kinetic equations to help clarify the release mechanism of the drug from the hot-melt enteric coated pellets [18].

RESULTS AND DISCUSSION

3.1 Evaluation of hot-melt enteric coated pellets: The results of the evaluation of pellets are summarized in [Table 2]. All the pellets prepared by extrusion-spheronization showed very good micromeric properties. Hot-melt coating of SA and PA over pellets resulted in further improvement of micromeric properties. The pellets had very good uniformity as desired and all formulations were within the size range of 800 to 1000 µm after HMC and exhibited a shape approaching that of a sphere. The surface was very smooth and pellet size distribution was narrow. Values of angle of repose were approximately 17-25° for all formulations shows good to excellent flow properties for coated pellets. Friability was negligible, having a maximum value of 0.23%. This value can be attributed to the loosening of some wax from the coating due to attrition of the friability test. Pellet hardness were measured with a dial type hardness tester was maximum around 1.8 kg/cm². Both friability and hardness values indicated that the pellets had good mechanical strength.
Table 2: Evaluation of uncoated and hot-melt enteric coated pellets.

<table>
<thead>
<tr>
<th>Form.⁵</th>
<th>Friability (%)</th>
<th>Hardness (kg/cm²)</th>
<th>Angle of Repose (°)</th>
<th>Bulk Density (g/cm³)</th>
<th>Tapped Density (g/cm³)</th>
<th>Hausner’s Ratio</th>
<th>Carr’s Index</th>
<th>Mean pellet Size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.21</td>
<td>1.4</td>
<td>23.84</td>
<td>0.83</td>
<td>0.94</td>
<td>0.117</td>
<td>1.133</td>
<td>0.865</td>
</tr>
<tr>
<td>F2</td>
<td>0.16</td>
<td>1.5</td>
<td>21.08</td>
<td>0.84</td>
<td>0.93</td>
<td>0.118</td>
<td>1.107</td>
<td>0.875</td>
</tr>
<tr>
<td>F3</td>
<td>0.09</td>
<td>1.7</td>
<td>19.98</td>
<td>0.86</td>
<td>0.96</td>
<td>1.041</td>
<td>1.163</td>
<td>0.895</td>
</tr>
<tr>
<td>F4</td>
<td>0.18</td>
<td>1.3</td>
<td>22.43</td>
<td>0.82</td>
<td>0.92</td>
<td>1.082</td>
<td>1.122</td>
<td>0.885</td>
</tr>
<tr>
<td>F5</td>
<td>0.13</td>
<td>1.5</td>
<td>19.36</td>
<td>0.84</td>
<td>0.94</td>
<td>1.061</td>
<td>1.119</td>
<td>0.900</td>
</tr>
<tr>
<td>F6</td>
<td>0.07</td>
<td>1.8</td>
<td>17.89</td>
<td>0.85</td>
<td>0.95</td>
<td>1.053</td>
<td>1.117</td>
<td>0.915</td>
</tr>
<tr>
<td>F0</td>
<td>0.23</td>
<td>1.3</td>
<td>24.96</td>
<td>0.78</td>
<td>0.89</td>
<td>1.235</td>
<td>1.141</td>
<td>0.840</td>
</tr>
</tbody>
</table>

Form.⁵ indicates formulation code.

3.2 Scanning electron microscopy (SEM): [Fig. 1-6] shows microphotograph and scanning electron micrographs of hot-melt enteric coated pellets. Scanning electron microscopic study was performed to study surface morphology of coated pellets. The scanning electron micrographs show a smooth surface and uniform coating. Pellets coated with PA were smoother and elegant in comparison with pellets coated with SA. The slight roughness of SA coated pellets may be due to premature solidification of SA leads to non-uniform coating pattern. However, the surface roughness was diminished by regulating temperature during coating operation and addition rate of melt combination.

Fig. 1: Photograph of stearic acid coated pellets of aspirin.

Fig. 2: SEM picture of stearic acid coated pellets of aspirin (30X).
Fig. 3: SEM picture of stearic acid coated pellets of aspirin (500X).

Fig. 4: Photograph of palmitic acid coated pellets of aspirin.

Fig. 5: SEM picture of palmitic acid coated pellets of aspirin (30X).
3.3 Determination of disintegration pH: The disintegration pH is that pH at which coated pellets show the highest amount of drug release at minimum fixed time. The material must be solubilized at alkaline pH to be considered suitable for enteric coating. Only results of 5% w/w wax coated pellets was suitable for this test and higher percent coatings that is 7.5% and 10% were not adequate for release from pellets [Fig. 7]. Due to lower extent of coating, an amount of the drug was also released at acidic pH. This might have been due to coating erosion and not solubilization as the core pellets were intact even after completion of the test. The drug release gradually increased with greater pH levels as can be seen in the graph. Contrary to previous studies however, the drug release, although increased, was not abrupt but instead showed a slow and steady rise in release [17]. This indicated that the PA and SA resist the gastric environment and will not release drug suddenly but gradually in the intestinal environment.

![Fig. 6: SEM picture of palmitic acid coated pellets of aspirin (500X).](image)

![Fig. 7: Effect of pH on disintegration of hot-melt coated pellets of 5% w/w stearic acid and palmitic acid as determined by drug release (mean ± SD, when sample size in triplicate).](image)
3.4 In vitro dissolution study: The dissolution study was carried out to determine the resistance of the materials namely SA and PA to the acidic environment of the stomach and their suitability as enteric coating materials. Ideally for enteric coating, there should be no release of drug in the acidic pH of the stomach, where this was determined in vitro by carrying out dissolution at 0.1 N hydrochloric acid for the first 2 hr. Dissolution was subsequently continued in pH 6.8 phosphate buffer. The drug release data of the dissolution study is shown graphically in [Fig. 8]. The gastric residence time of non-disintegrating pellets (diameter 1 to 2 mm) under fasting conditions has been shown to be from 0.4 to 2 hr, with a mean of 1.2 hr [13, 16]. Intestinal transit times for different dosage forms, independently of diameter, are 2 to 4 hr with a mean of 3 hr [19, 20]. Therefore it can be concluded that, the most of the pellet formulation should be at the end of the small intestine 4 hr after drug administration [17].

![Graph](image)

**Fig. 8: Dissolution study of enteric coated pellets (mean ± SD, sample size in triplicate).**

The [Fig. 8] indicates that both SA and PA exhibit very good enteric coating ability. Negligible amount of drug was released in acidic pH at the lower coating level of 5% w/w, whereas at a higher coating level there was practically zero drug release from the pellets. As the pellets were transferred to the higher pH level of 6.8, there was an abrupt increase in release of the drug from the pellets. This release was dependent upon coating extent. Significant differences were noted in the drug release pattern of the pellets containing 5 and 10% wax coat. This suggests that it is possible to retard drug release or extend lag time in relation to commencement of drug absorption by making the coat thicker at 10% rather than 5%. This is contrary to the findings with conventional enteric polymers (Aqoat AS-HF) as this polymer shows no significant effect of coatings above a 15% level [17]. This might be due to the inherent property of materials evaluated and their solubility mechanism. SA and PA first undergo saponification at higher pH and then become dissolved; it takes longer to dissolve the coat and increase drug release.

3.5 Kinetic data analysis: The release kinetics study according to goodness of fit shows that the majority of formulation follows Higuchi model hence drug release mechanism concluded as diffusion for both waxes [Table 3]. For F1 and F4 formulations the 'n' values of Korsmeyer-Peppas equation lies between 0.5-1, hence more precisely drug release mechanism is non-Fickian diffusion (anomalous transport). The 'n' values shows mechanism of drug release from coated pellets was diffusion coupled with erosion. The close proximity of coefficient of correlation indicates that no single mechanism was completely dominant and it confirmed that release was governed by more than one mechanism.
Table 3: Correlation coefficients ($r^2$) for Hot-Melt Enteric coated aspirin pellets

<table>
<thead>
<tr>
<th>Form. Code</th>
<th>Zero order $k_0$</th>
<th>$r^2$</th>
<th>First order $k_1$</th>
<th>$r^2$</th>
<th>Higuchi $r^2$</th>
<th>Peppas $r^2$</th>
<th>Hixon-Crowell $n$</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>21.17</td>
<td>0.865</td>
<td>-1.1791</td>
<td>0.836</td>
<td>0.877*</td>
<td>0.839</td>
<td>0.73</td>
<td>0.641</td>
</tr>
<tr>
<td>F2</td>
<td>20.25</td>
<td>0.917</td>
<td>-1.1690</td>
<td>0.872</td>
<td>0.929*</td>
<td>0.898</td>
<td>1.22</td>
<td>0.838</td>
</tr>
<tr>
<td>F3</td>
<td>18.21</td>
<td>0.924</td>
<td>-1.1168</td>
<td>0.891</td>
<td>0.925</td>
<td>0.993*</td>
<td>1.69</td>
<td>0.971</td>
</tr>
<tr>
<td>F4</td>
<td>21.23</td>
<td>0.849</td>
<td>-1.1906</td>
<td>0.832</td>
<td>0.859*</td>
<td>0.705</td>
<td>0.55</td>
<td>0.628</td>
</tr>
<tr>
<td>F5</td>
<td>20.63</td>
<td>0.902</td>
<td>-1.9561</td>
<td>0.865</td>
<td>0.971*</td>
<td>0.861</td>
<td>1.01</td>
<td>0.795</td>
</tr>
<tr>
<td>F6</td>
<td>19.01</td>
<td>0.934</td>
<td>-1.1906</td>
<td>0.887</td>
<td>0.942</td>
<td>0.985*</td>
<td>1.39</td>
<td>0.958</td>
</tr>
</tbody>
</table>

Where, Form. indicate formulations
Aristicks (*) indicates best fitted model.

CONCLUSION
The present study indicates that both the hot-melt coating agents (PA and SA) were found to have excellent enteric coating ability. At 5% w/w wax coating level, negligible amounts of drug were released in the acidic environment after 2 hr. At and above a 7.5% w/w coating, practically zero drug release was observed in acidic pH. With increased coating level slower the rate of drug release was observed. The results of the present study shows that present hot-melt coating materials can constitute an excellent option to conventional enteric coating polymers. The hot-melt coating technique can be an efficient, eco-friendly and economical tool for formulating enteric coated pellets.

REFERENCES
15. Gandhi R, Lal KC, Panchagnula R. Extrusion and spheronization in the development of


