DEVELOPMENT AND EVALUATION OF ORAL CONTROLLED RELEASE FROM ACECLOFENAC SODIUM PELLETS

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ABSTRACT
The objective of the present study was to prepare the pellets loaded with aceclofenac sodium (ACS) as model drug through pellitization technique by using the blend of Sodium alginate (SA) and glyceryl palmito stearate (GPS) as hydrophilic and hydrophobic carriers, along with Methyl crystalline cellulose (MCC) as spherizer enhancer in various concentrations and examines the influences of various process parameters of drug containing pellets. This system was able to prolong the drug release, minimizing the drug related adverse effects and improve bioavailability in different GI-tract conditions. Formulated drug loaded pellets were investigated for physicochemical properties and drug release potential. Scanning electron microscopy (SEM) photographs and calculated sphericity factor confirms that the prepared formulations were spherical in nature. The drug contain pellets were stable and compatible, as confirmed by DSC and FTIR studies. The release of drug was controlled for more than 24 h. Intestinal drug release from pellets was noticed and compared with the releases behavior of commercially available formulation Aceton SR®– 100 mg tablet. The rate of drug release followed first order kinetics and the mechanism of drug release followed Fickian diffusion. The drug release performance was greatly affected by the materials used in pellets preparations, which allows absorption in the intestinal tract by a controlled manner.

Keywords: Pelletization, Aceclofenac sodium, Aceton SR®– 100, release kinetics.

INTRODUCTION
In recent years a wide variety of newer oral drug delivery systems like controlled /sustained release dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects [1]. Aceclofenac sodium
Aceclofenac sodium is a newer derivative of diclofenac and having less GIT complication. It is rapidly and completely absorbed after oral administration. Administration of aceclofenac was reported to induce adverse side effects on GIT as well as hepatic, pancreatic, renal, endocrine, nervous, cardiac and hematological systems, along with the short half-life (3-4 hours) has led to the design of controlled release formulation of aceclofenac.To achieve maximum therapeutic effect with a low risk of adverse effects, controlled released preparations are preferred. The side effects could be lowered by controlling the drug release and by adjusting the absorption rate. This can be achieved by employing suitable modifications in the manufacturing process.

Extensive clinical experience and well-controlled studies have shown that aceclofenac is more effective than piroxicam in the treatment of minor traumas and phlogistic infections of soft tissues. Evidence have shown in the recent years that hydrophilic and hydrophobic carriers materials have the physical properties suitable to prepare gastro resistant, biocompatible, biodegradable matrix pellets to release the entrapped drug in the intestinal lumen. In the present study, a novel extrusion/spheronization meltable dispersion emulsified cooling induced solidification method was employed using inert hydrophilic and hydrophobic carriers material and nontoxic solvents to load the drug into pellets. Sodium alginate (SA) is a natural polymer is very promising and has been widely exploited in pharmaceutical industry, because of its tailor – made to suit the demands pf applications. SA has the advantages of being nontoxic orally, high biocompatibility, and inability to reswell in acidic environment, whereas they easily reswell in an alkaline environment. So acid sensitive drugs incorporated into the beads would be protected from gastric juice. The chief characteristic of sodium alginate is impermeability to gastric juices but susceptibility to intestinal juices. ACS should be dosed 100 mg twice a day. Due its low therapeutic index, the frequency of adverse effects may be dose related. As demonstrated by pharmacokinetick studies on ACS, the oral administration of a single controlled release enteric coated tablet is effective even when administered once a day these findings suggested that kinetic control is effective for preventing the untoward effects of ACS. Types and nature of the
lipid was found strongly affect the drug release mechanisms \cite{11,13}. Moreover, the drug administered thrice a day in a conventional dosage regime which consumes valuable time as far as the physician, patient and pharmacist concerned. When finely divided drug particles dispersed in lipid carriers, responsible for crystallization upon storage under humid condition was resulting in changes in drug dissolution and bioavailability \cite{14}. Dispersion of finely divided poorly water soluble drug in lipidic carriers is an interesting technique for the production of matrix pellets. Different methods were applied for the preparation of lipidic matrix based pellets by extrusion – spheronization \cite{15,16}. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously.

A thorough literature search revealed a lack of information on combination of hydrophilic SA and hydrophobic glyceryl palmito stearate (GPS) based pellets for controlled drug release, using spheronizer enhancer MCC and Sodium lauryl sulphate (SLS) (0.3 % w/v) as leachable pore forming and wetting agent. GPS act as an inert matrix and drug released very slowly as compared to hydrodispersible, hydrophilic matrix gelucire 50/13. GPS reported as a solidifier, controls the drug release, protects the hygroscopic substances and facilitates the incorporation of liposoluble active ingredients and preservative for lipids, oils, waxes and solvents \cite{17}. MCC was incorporated in most formulations via extrusion-spheronisation, because it enhanced the rheological properties of the wetted mass, resulted good sphericity, low friability, high density and smooth surface for successful extrusion-spheronisation \cite{18,19}. In the present study controlled release pellets were developed by extrusion-spheronization of an ACS/SA / GPS with addition of MCC with SLS to tailor drug release. The aim was to develop ACS suitable for once daily formulation and examine the influences of various process parameters on physicochemical properties of pellets and drug release potential.

**MATERIAL AND METHODS**

**Materials**

Aceclofenac sodium (ACS) was obtained from M/s Microlabs Bangalore, India, as gift sample. It is a white to almost white crystalline powder with a bitter taste. It is insoluble in water; soluble in alcohol and methyl alcohol and freely soluble in acetone and dimethyl formamide. Sodium alginate was procured from Loba Chemie Pvt Ltd,
Mumbai, India. It is a white to yellowish brown filamentous, grainy, granular or powdered forms of the sodium salt of alginic acid. It is used as gelling agent, emulsifier, stabilizer and thickener to increase viscosity in food industry, also used in indigestion tablets and the preparation of dental impressions. Microcrystalline cellulose pH 101 (MCC) was procured from Signet Chemicals, Mumbai, India. It is a white colourless, odorless, tasteless and crystalline powder. Glyceryl palmito stearate (GPS- Precirol ATO 5), Sodium lauryl sulphate (SLS) and microcrystalline cellulose (MCC) were procured from Loba Chemie, Mumbai, India. Solvents and chemicals were of analytical grade.

**Preparation of pellets**

The pellets were prepared by pelletization technique using extrusion / spheronization method. ACS, SA, GPS and MCC were passed through sieve No. 40 prior to pelletization and mixed uniformly in a planetary mixer. The bubble free SLS 80 (0.3 %) solution was added dropwise to the mixture and mixed for 30 min. The obtained good dough mass was extruded using a piston extruder (1 mm orifice, Kalweka, India). The extrudates were immediately spheronized for 5 min at a rotational speed of 750 rpm and an air velocity of 1 kg/cm². The pellets were dried over night at room temperature and cured at 40 °C for 24 h in a fluid bed dryer (Kothari, India). Five batches of drug loaded pellets were prepared to investigate the effect of certain formulation and process variables, such as drug to blend of polymer ratio, concentration pore forming agent, spheronization speed and time on the mean particle size, yield and in-vitro drug release.

**Characterization and evaluation of pellets**

**Particle size analysis**

The particle sizes of drug loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Olympus model (SZX-12) having resolution of 40 x was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to...
1/30mm (33.33μm). In all measurements at least 20 particles in five different fields were studied. Each experiment was carried out in triplicate.

**Measurement of micromeritic properties**

Angle of repose (θ) was assessed to know the flowability of matrix pellets, by a fixed funnel method using the formula;

\[
\tan (\theta) = \frac{\text{height}}{\text{radius}} \quad \ldots \ldots (1)
\]

Tap density and bulk density of the pellets were determined using tap density tester. The percentage Carr’s index (I, %) was calculated using the formula;

\[
\text{Carr’s index (I, %)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \quad \ldots \ldots (2)
\]

Granule density of the pellets was determined by displacement method using petroleum ether.

\[
\text{Granule density} = \frac{\text{Weight of pellets}}{\text{Volume of petroleum ether displaced}} \quad \ldots \ldots (3)
\]

The Hausner ratio of the matrix pellets was calculated using the formula;

\[
\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \ldots \ldots (4)
\]

The friability test was performed on the pellets to ensure their mechanical strength. Lower friability values indicate good mechanical strength. Pellets of known mass (1000 – 1400 m) were placed in a Roche Friability tester (Electro lab Friability tester, EF -2) and subjected to impact testing at 25 RPM for 5 min. Pass the pellets through a sieve of mesh size 16 (1000μm), weight of pellets retained on the sieve was noted and the friability was calculated using the following equation;

\[
\text{Friability (\%)} = \left[1 - \frac{\text{initial weight}}{\text{weight retained after 100 rotations}}\right] \times 100 \quad \ldots \ldots (5)
\]

**Scanning electron microscopy analysis (SEM)**

The shape and surface characteristics were determined by scanning electron microscopy (model-LV 5600, jeol, USA and photomicrographs were recorded, by suitable magnification at room temperature. In order to determine the sphericity of the pellets, the tracings of pellets (magnification 45 X) were taken on a block paper using camera lucida (model -Prism type, Rolex, India) and circulatory factor was calculated using the equation;

\[
S = \frac{p^2}{(12.56 \times A)} \quad \ldots \ldots (6)
\]

where, A is the area (cm²) and p is the perimeter (cm).

**Differential scanning calorimetry (DSC)**
DSC studies were carried out to study the thermal behaviors of drug alone and mixture of drug and polymer using Du Pont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with the help of an empty cell (high purity alpha alumina disc) as the reference. The instrument was calibrated using high purity indium metal as standard. The DSC scans of the samples were recorded in the temperature range ambient to 156° C in nitrogen atmosphere at a heating rate of 10° C /min.

**Fourier transform- infrared spectroscopic analysis (FT-IR)**

Drug polymer interactions were studied by FT-IR spectrophotometer (Shimadzu, 8033, USA) by KBr pellet method. The IR- spectrum of the pellet from 450- 4000cm-1 was recorded.

**Determination of drug content**

For determination of drug content, 100 mg pellets were dissolved in 100 ml of methanol. The resulted solution was analyzed spectrophotometrically at 274 nm (Shimadzu-1601, Japan) after suitable dilution with phosphate buffer (pH 7.4) \[^{[21]}\].

**Loose surface crystal study (LSC)**

This study was conducted to estimate the amount of drug present on the surface of the pellets and 100mg of pellets were suspended in 100ml of phosphate buffer (pH 7.4). The samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 274 nm. Percentage of drug released with respect to entrapped drug in the sample was recorded.

**In vitro drug release studies**

USP XXI dissolution apparatus, type II was employed to study the percentage of drug release from various formulations prepared. Accurately weighed quantities of drug (aceclofenac - 100 mg equivalent to a commercial preparation – Aceton SR\(^{\circledR}\) – 100 mg tablet) and drug loaded pellets of each batch were taken in 900 ml dissolution medium and drug release was studied (aceclofenac – 2 hrs in pH 1.2, hydrochloric acid buffer and 6 hrs in pH 7.4, phosphate buffer) at 100 rpm and at a temperature of \(37 \pm 0.5 \) °C. 10 ml of dissolution medium was withdrawn periodically using guarded sample collectors at regular intervals (30 min for first 4 h and at 60 min intervals for the next 20 h), the sample (10 ml) was withdrawn and replaced with same volume of fresh medium. The withdraw sample were filtered through a 0.45μm membrane filter and after appropriate
dilution using guarded sample collectors, then estimated for ACS concentration spectrophotometrically. The release data was analyzed using PCP dissolution - V2 – 08 and Graph Pad Instat software. The data, thus obtained was fit into Peppas model. The various parameters the intercept A, the release constant K and regression coefficient R² were calculated. A differential factor (f₁) and similarity factor (f₂) were calculated from dissolution data according to the following equations;

$$f_1 = \frac{\sum_{t=1}^{n} |R_t^R - R_t^T|}{\sum_{t=1}^{n} R_t^R} \times 100$$  \hspace{1cm} (7)$$

$$f_2 = 50 \log \left\{ 1 + \left( \frac{1}{n} \right) \sum_{t=1}^{n} (R_t^R - R_t^T)^2 \right\}^{-0.5} \times 100$$  \hspace{1cm} (8)$$

Where, f₁ - differential factor, f₂ - similarity factor, n – number of time point, Rt – dissolution value of the reference at time, ‘t’ and Tt - dissolution value of test formulation at time ‘t’. Differential factor, f₁ was calculated by the percentage difference between the two curves at each time point and measured the relative error between the two curves. The acceptable range for differential factor, f₁ is 0 -15. The similarity factor, f₂ was logarithmic reciprocal square root transformation of the sum-squared error and is a measure of the similarity in the percentage dissolution between the reference and test products. If dissolution profile to be considered similar, the values for f₂ should be in the range 50 - 100.

**Stability studies of pellets**

After determining the drug content, the optimized drug contain pellets were charged for the accelerated stability studies according ICH guidelines. To assess stability, accurately weighed drug contain pellets equivalent to 100mg of Aceclofenac sodium were filled into a hard gelatin capsules manually and sealed in a aluminum packaging coated inside with polyethylene. The studies were performed at 40 ± 2°Cand 75 ± 5% relative humidity (RH) in the desiccators with saturated salt solution for up to 90 days. A
visual inspection and drug content estimation was conducted every 15 days for the entire period of stability study. Drug content was estimated spectrophotometrically at 274 nm.
RESULTS AND DISCUSSION

Evidence have shown in the recent years that lipidic materials have the physical properties and behavior suitable to prepare matrix pellets to release the entrapped drug into gastro intestinal tract \cite{19,22}. In the present study, blend of SA, GPS and MCC formulated as pellets by different ratio using non toxic solvent, presented in Table 1. The present method is quite different from that reported by Siepman et al \cite{23}, because, none of them succeeded to formulate pellets by blend of SA, GPS and MCC by extrusion–spheronization technique. In the present study, examines influences of various process parameters on physicochemical properties and drug release potential from pellets have been studied.

Incorporation of drug into different ratios of SA blend affects the physical appearance of the pellets was observed. In the present study the formulation F5 having the optimum drug and SA blend ratio (30: 10: 05: 55) suitable to produce solid, discrete, spherical, free flowing pellets and having a sufficient mechanical strength. Resultant pellets did not have any surface irregularities and they are non aggregated. It was found that the higher the ratio of drug used (30, 40 and 50 % w/w) SA blend were produced aggregate pellets masses during spheronization and resulted pellets were unsuitable for pharmaceutical uses. SEM photographs also indicated the presence of the drug crystals on the surface of the pellets. Because surface accumulated drug resulting in burst release and impossible to control the drug release from the pellets during dissolution.

In the present study, optimized ratio of 10 % w/w of SA was used to produce spherical pellets. It was found that higher ratio of SA (> 10 % w/w) or decreased ratio of SA (< 10 % w/w), the produced pellets were not spherical and impossible to distinguish as individual pellets. In order to avoid the formation of irregular shaped pellets, an optimum of 10 % w/w ratio was used to prepare pellets. To obtain optimal concentrations of GPS, concentrations ranging from 1 to 5 % w/w of the total formulations were investigated. In the present study, optimum concentration, 5% w/w of GPS was used to produce better pellets.

In order to obtain optimal concentrations of pore forming agent, various concentrations of aqueous solution SLS ranging from 0.1 to 1.0 % w/w of the total
formulations were investigated. But 0.1 to 0.5 % of aqueous solution SLS failed to produce required pores in the pellets. When more than 0.6 % w/w aqueous solution SLS was used, resultant pellets contains sufficient numbers of pores. In the present study, optimum concentration, 0.6 % w/w of aqueous solution SLS was used as pore forming agent in the pellets.

Incorporation of hydrophilic (SA) into lipophilic (GPS) polymer requires the addition of wetting agent at an optimum concentration of aqueous solution of SLS (9 ml of 0.6 % w/w) to reduce the interfacial tension between SA and GPS. An attempt was made to prepare wet mass without the addition of wetting agent. But the process was failed and as it resulted, in an aggregate cake like mass during the pelletization. It may due to repulsion resulting between GPS and MCC. It was found that hydrophilic and lipophilic balance (HLB) value of SLS is 40, found to be more suitable to increase substantial dispersion of drug in SA blend. It was also noticed that 9 ml of aqueous solution of SLS (0.6 % w/v) was used as wetting agent, produced pellets were spherical, free flowing, free from surface irregularities. As the volume of aqueous solution of SLS was more than 9 ml, resultant pellets were sticky, aggregate, and impossible to produce spherical shaped pellets. As the volume of the aqueous solution of SLS was less than 9 ml, requires more pressure for pelletization and difficult to separate as an individual pellets. Hence, the changes in volume of SLS solution as wetting agent affects the sphericity of the pellets, was confirmed by SEM photographs (Fig. 1 a).

The important factor that influences the size distribution of pellets was the spheronization speed and residence time. A spheronization speed of 200 rpm and residence time 6 min was used to obtain reproducible and uniform sized pellets. As increase in spheronization speed from 50 to 200 rpm, a change in the shape and size of
the pellets were noticed. When the spheronization speed was 50, 100, 150 rpm produces rod, egg and semi spherical shaped pellets respectively. Increased spheronization speed from 200 to 300 rpm, a reduction in the average sizes and recovery yield of the pellets was observed. Spheronization speed was lower than 200 rpm, larger and irregular shaped pellets were formed and not suitable for pharmaceutical purpose. It was found that 200 rpm was optimized condition to produce discrete, spherical, hard and free flowing solid pellets. Spheronization time also affects on the pellet shape and size (Table 1). It was also found that an increase in spheronization residence time from 3 to 6 min (at a stirring speed of 200 rpm) resulted in changes in the shape and size of the pellets. From the study, optimized spheronization time was found to be 5 min, suitable to produce spherical, hard and free flowing solid pellets. However, further increases in spheronization time considerably affect the pellet shape and size. Hence, to produce required shape and sizes of the pellets, optimum spheronization speed (200 rpm) and spheronization residence time (6 min) was used.

In the present study, MCC posses a good extrusion aid at optimal concentrations of 55 %, influences the mean diameter of the pellets. Due to good binding properties of MCC, it provides cohesiveness to a wetted mass, able to retain a large quantity of binding agent helps to provide large surface area. Hence the optimal concentrations of MCC also improves the plasticity of wetted mass and enhancing spheronization by preventing phase separation, during extrusion spheronization was observed. A similar optimal concentration of MCC was reported [21].

**TABLE 1: FORMULATION CHART OF ALL THE FORMULATIONS**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Formulation</th>
<th>Parameters</th>
<th>Description of pellets</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS:SA:GPS:MCC (w/w %)</td>
<td>F1</td>
<td>30 : 30 : 01 : 39</td>
<td>Rod shape and brittle</td>
</tr>
<tr>
<td></td>
<td>F2</td>
<td>30 : 25 : 02 : 43</td>
<td>Egg shape and brittle</td>
</tr>
<tr>
<td></td>
<td>F3</td>
<td>30 : 20 : 03 : 47</td>
<td>Semi spherical and brittle</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>30 : 15 : 04 : 51</td>
<td>Spherical and brittle</td>
</tr>
<tr>
<td></td>
<td>F5</td>
<td>30 : 10 : 05 : 55</td>
<td>Spherical and hard</td>
</tr>
<tr>
<td>Spheronization speed (rpm)</td>
<td>F5</td>
<td>50</td>
<td>Rod shape</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>Egg shape</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150</td>
<td>Semi spherical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200</td>
<td>Spherical</td>
</tr>
<tr>
<td>Spheronization duration</td>
<td></td>
<td>3</td>
<td>Rod shape</td>
</tr>
</tbody>
</table>
Sieve analysis data (Table 2) indicates that the prepared pellets were in the size range of 1024 to 1212 μm and 69.3 to 71.5 % were of pellet size was 1212 μm. It was found that higher ratio of SA (> 35 % w/w) in the pellets did not influence significantly either the average diameter of the pellets or their size distribution. Hence, produced pellets were in the desired size proving that the adopted process is reproducible.

Generally multi particulate drug delivery systems are formulated as single dosage form (in the form of capsule or tablet), such systems posses better and adequate micromeritic properties (Table 2). The values of angle of repose (θ°) for the pellet were in the range 25.13 - 27.23 indicating good flow potential for the pellets. The measured tapped density (0.821 to 0.896 g/cm³), granule density (1.024 to 1.076 g/cm³), % Carr’s index (8.45 to 9.56%), and Hausner ratio (1.023 to 1.165), were well within the limits, which indicates good flow potential for the prepared pellets. The friability of the ACS pellet formulations was found to be in the range 0.39 - 0.53 % and it falls in the expected range (less than 5% as per FDA specification). Friability is measured to assess the mechanical strength of the pellets in terms of fragmenting or powdering during filling operation into capsule shell. As the ratio of MCC and GPS higher, friability of the was increased (Table 2). Additionally, pellets cured at 40°C for 24 h produces pellets with good mechanical strength due to low moisture content. As the curing temperature increases (45°C for 24 h), friability of the pellets found to decreases and pellets having shrunk porosities was observed, due to loss of moisture content. When the pellets cured below 40°C for 24 h, produced pellets were dumbbell shaped with protruding...
surfaces (confirmed from SEM photomicrographs) and these pellets not suitable for pharmaceutical purpose.

SEM photomicrographs (Fig.1 a), showed that the pellets (formulation F5) were spherical in nature and had a smooth surface when they cured at 24 h at 40°C. SEM photomicrographs of the pellets reveal the uniform distribution of the drug in the pellets. Figure 2 (b) shows the SEM photomicrographs of the surface of the pellets and presence of fine pores (F5). The formed fine pores on the pellets can be clearly observed. When the pellets were cured at 24 h for 45°C, surface inward dents and shrinkage were observed (collapse of the wall of the pellets), which might be due to drop in residual moisture content from pellets. The drug crystals observed on the surface as a result of their migration along with water to the surface during drying. This result clearly indicates that influence of moisture content on surface morphology of the pellets [23].
TABLE 2: YIELD, SIZE DISTRIBUTION, MICROMERITIC PROPERTIES OF ALL ACS/SA/GPS/MCC PELLET FORMULATIONS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Yield (%)</th>
<th>Average size (μm)</th>
<th>Angle of repos θ₀</th>
<th>Tapped density (g/cm³)</th>
<th>Granule density (g/cm³)</th>
<th>Carr’s index (%)</th>
<th>Hausner ratio (%)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>91.22</td>
<td>1024</td>
<td>27.23</td>
<td>0.821</td>
<td>1.024</td>
<td>8.91</td>
<td>1.023</td>
<td>0.39</td>
</tr>
<tr>
<td>F2</td>
<td>92.80</td>
<td>1087</td>
<td>26.12</td>
<td>0.854</td>
<td>1.056</td>
<td>8.65</td>
<td>1.165</td>
<td>0.42</td>
</tr>
<tr>
<td>F3</td>
<td>93.12</td>
<td>1134</td>
<td>25.13</td>
<td>0.828</td>
<td>1.054</td>
<td>8.45</td>
<td>1.145</td>
<td>0.45</td>
</tr>
<tr>
<td>F4</td>
<td>94.45</td>
<td>1189</td>
<td>26.43</td>
<td>0.873</td>
<td>1.076</td>
<td>8.78</td>
<td>1.098</td>
<td>0.49</td>
</tr>
<tr>
<td>F5</td>
<td>96.76</td>
<td>1212</td>
<td>26.23</td>
<td>0.896</td>
<td>1.032</td>
<td>9.56</td>
<td>1.123</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*a Standard deviation n = 3

Figure 1

SEM photomicrographs of; (a) ACS loaded pellet in spherical shape (F5), (b) ACS pellets showing surface pores (F5)

The calculated sphericity values of the pellets nearer to the value 1, confirmed the prepared pellets were spherical in nature. Interestingly, pellets cured for 24 h at 40°C the sphericity values of the pellets nearer to the value 1, whereas pellets cured for 24 h at 45°C, obtained sphericity values ranged between 1.16 -1.25 (pellets were shranked and elongated form). The removal of residual moisture content from pellets during curing exerts an influence on the morphology of the final product 23.
The IR spectra of the ACS and drug contain pellets (formulation F5) were found to be identical and presented (Fig. 2). The characteristic IR absorption bands noticed for ACS are at 1282.57 cm\(^{-1}\) due to C-N stretching, 3271.05 cm\(^{-1}\) due to N-H stretching, 1415.65 cm\(^{-1}\) due to C=C aromatic stretching and 1253.64 cm\(^{-1}\) due to C-O stretching were present in all formulations. The FTIR spectra of the pure drug and formulation F5 indicated that characteristics bands of ACS were not altered without any change in their position after successful encapsulation, indicating no chemical interactions between the drug and carriers used. However, a slight shift in the position of the absorption peaks was noticed. This result showed that a minor physical interaction might have occurred between drug and polymers [24].

![Figure 2](image)

**Figure 2**
FTIR spectra of pure drug and optimized formulation (F5)

DSC scans were recorded for ACS and formulation (F5). A representative thermogram of the ACS and optimized formulation (F5) is shown in Figure 3. The pure ACS displayed a single sharp endothermic peak at 155.41° C corresponding to the melting point of the drug and identical peak was observed at 155.41° C in the ACS formulation (F5). This result clearly indicated that the drug retains its identity in the
formulation (F5). The additional peak in the formulation (F5) in the DSC thermograms was noticed. This is an agreement with literature findings [24].

![DSC thermograms of pure drug and Optimized formulation (F5)](image)

**Figure 3**

DSC thermograms of pure drug and Optimized formulation (F5)

Drug content in all the formulations were in the range of 97.42 - 96.89 % w/w. Drug content was least in formulation F1 (96.89 % w/w) and high for formulation F5 (97.42 % w/w). It is evident that, the drug content increases with increased in pellets size (1024 to 1212 μm). This might be due to increased relative surface area of the pellets, leads to more drug content.

Loose surface crystal (LSC) study was an important parameter to know the amount of drug deposited on the surface of the pellets without proper distribution. With increasing concentrations of SA, LSC decreased significantly.

In vitro release studies were carried out for the formulations in both acidic and basic media to stimulate in vivo conditions. Drug release profile from pellets was a biphasic manner, consisting of initial fast release followed by a slow release. This result could be attributed to the dissolution of the drug present initially at the surface of the pellets and rapid penetration of dissolution media from the matrix structure. The higher amount of ACS released was observed from formulation F5 (96.23%) as compared to all other formulations F1 (85.34 %), F2 (86.23 %), F3 (87.98%) and F4 (88.78 %). This result clearly indicates that lowered drug release was noticed for the systems containing
higher content of SA. Because higher water swellable SA particles forms higher viscosity, retards the penetration of dissolution media into pellets, thus limiting the drug release from pellets. This typical behavior was commonly observed in diffusion controlled drug delivery systems [24].

The drug release profile obtained for formulation F5 indicated that it is an ideal formulation for administration for every 24 h, as it released 96 % of the embedded drug in 24 h. In this investigation author made an attempt to prepare the pellets with lower levels of SA and higher concentrations of aqueous SLS solution (0.9 % w/w), pellets exhibited initial burst release of drug. This result could be attributed to the dissolution of drug present initially at surface of the matrices and rapid penetration of dissolution media into pellets matrix structure. However, the formulations exhibited little burst effect at higher levels of SA. Further increased SA amount, formed thicker gel around the pellets, strongly inhibiting the dissolution media penetration, resulting in significant reduction in the drug release. This finding indicated a considerable release retarding potential of the drug from pellets by varying ratios of SA / GPS /MCC and pore former.

The effect of curing of pellets at different temperature ACS release from SA / GPS / MCC pellets was studied. Interestingly pellets cured at 40°C for 24 h showed controlled drug release. Drug release upon curing at 40°C (24 h) might be due to residual moisture content present in the pellets. This result indicates that the moisture present in the pellets reduces the cohesive force, which facilitates the wetting of pellets and increased the pellets disintegration (confirmed visually). Pellets cured above 45°C for 24 h, showed the least drug release, due to least amount of residual moisture content present in the pellets responsible for low wettability. Drug contain pellets are softened and produced a denser structure, less permeable for dissolution media, delayed the disintegration of pellets (confirmed by visual observation). This result clearly indicates drug delivery from SA/GPS/MCC pellets depends on curing conditions and moisture content.

To better understand the morphology of the pellets and potential changes occur after exposure to the release media was observed by microscopy. Fig.4 shows photographs of ACS loaded pellets before and after 2 h exposure to 0.1N HCl and phosphate buffer pH 7.4 respectively. It is evident that the pellets were initially spherical
in shape and there was no change occurred up to 30 min exposure (Fig. 4a). But pellets started to lose their edges slowly by disintegration after exposed to 0.1N HCl ((Fig. 4b) for 2 h. When pellets exposed to phosphate buffer pH 7.4 (after 2h), the edges of the pellets start to disintegrate rapidly and resulting in drug release.

Pellets prepared by using optimal concentrations of aqueous SLS solution (9 ml of 0.6 % w/v), 96% of the embedded drug were released over 24 h. It was observed that the pellets prepared by using more or less than the optimal concentration solution, fail to release the drug from pellets in a controlled manner. The rate of drug release followed first order kinetics and numerical data fitted into Peppa’s equation \(^{21}\). Statistically estimated values of n of drug from pellets at 95 % confidence limit, is lie in the range 0.35 – 0.42 for formulation F1-F5 studied and 0.40 for Aceton SR® – 100 mg tablet, indicated that the drug release from the formulations F1 – F5 and Aceton SR® – 100 mg tablet was Fickian diffusion. In our experiments the result of n clearly indicates that the diffusion is the dominant mechanism of drug release from these formulations. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid depending on the concentrations of the SA. As gradient varies, the drug is released, and the distance for diffusion increases. From this it was noticed that drug diffuses at a slower rate as the distance for diffusion increases. This is a good agreement with literature findings\(^{25}\). The obtained correlation coefficient, \(R^2\) for the ACS pellets lies in the range of 0.946 – 0.995. The same result was noticed for Aceton SR® – 100 mg tablet (0.996).

The drug release profiles of the optimized formulation F5 was the same that of release profile of oral formulation Aceton SR® – 100 mg tablet. The plot of the cumulative percent drug release as a function of time for formulation F5 and Aceton SR® – 100 mg tablet is shown in Fig 5. From the figure, it is evident that the drug was controlled from ACS pellets controls than the commercially available product Aceton SR® – 100 mg tablet.
Differential factor ($f_1$) and similarity ($f_2$) factor was calculated from dissolution profile and the results were compared to the formulation, F5 and Aceton SR®– 100 mg tablet. The differential factor ($f_1$) and similarity factor ($f_2$) obtained from dissolution profile indicates that the formulation F5 (8.32, 9.03) and Aceton SR®– 100 mg tablet (75.67, 76.98) were similar.

The calculated diffusivity values are given in Table 3. From the table it is noticed that, diffusivity values of trial 1 (without SA) is quite high, since there is no barrier to control the drug release. The values of F1 and F2 are quite low, due to fewer amounts of GPS, MCC and more amount of SA, resulted in less solubility of drug in aqueous media. On the other hand, the diffusivity values for formulations F3 and F4 was slightly higher. This is due to fact that more ratio of GPS, MCC and less ratio of SA, so the drug diffuses easily into the external environment. Formulation F5, which showed optimum drug release during the in vitro dissolution studies, exhibited a higher diffusivity. It also
supports the fact that the drug is easily diffusible through the pores formed in the pellets membrane.

**TABLE 3: DIFFUSIVITY DATA OF ALL SA/GPS/MCC PELLETS**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$D_1 \times 10^9$ (cm$^2$/s)</th>
<th>$D_2 \times 10^9$ (cm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1 (without GPS)</td>
<td>1.43</td>
<td>1.32</td>
</tr>
<tr>
<td>F1</td>
<td>0.48</td>
<td>0.38</td>
</tr>
<tr>
<td>F2</td>
<td>0.53</td>
<td>0.50</td>
</tr>
<tr>
<td>F3</td>
<td>0.64</td>
<td>0.62</td>
</tr>
<tr>
<td>F4</td>
<td>0.73</td>
<td>0.69</td>
</tr>
<tr>
<td>F5</td>
<td>0.94</td>
<td>0.88</td>
</tr>
</tbody>
</table>

*a Standard deviation n = 3,

The optimized formulation F5 was subjected for accelerated stability studies. Stability studies were carried out 40°C ± 1°C and 75% ± 5% relative humidity for a period of 90 d (Table 4). It was observed that, no significant change in the drug content from the pellets was observed. It is evident from the table that, formulations F5 exhibited good stability during investigation period, which indicates the drug was in stable form.

**TABLE 4: ANALYTICAL STABILITY STUDY RESULTS OF OPTIMIZED PELLETS (F5) STORED AT 40°C AND 75% RH**

<table>
<thead>
<tr>
<th>Sampling duration (days)$^a$</th>
<th>Drug content (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97.42</td>
</tr>
<tr>
<td>15</td>
<td>97.40</td>
</tr>
<tr>
<td>45</td>
<td>97.39</td>
</tr>
<tr>
<td>90</td>
<td>97.38</td>
</tr>
</tbody>
</table>

*a Standard deviation n = 3

**CONCLUSIONS**

The objective of the study was to prepare and evaluate ACS contain pellets by the process of extrusion followed by spheroidization for controlled release. The method employed was economical and does not imply the use of toxic solvents. The aqueous SLS, which forms micropores on the surface of the pellets. The results of micromeritic properties, hausner ratio and friability of the pellets were well within the limits which indicate good flow potential for the prepared pellets. Drug contains pellets exhibited
spherical nature as evidenced by SEM photomicrographs and sphericity studies. From the FTIR and DSC studies, it was observed that there was no chemical interaction between the drug and polymers used indicates that drug was in stable form. The drug content study revealed uniform distribution of the drug in the pellets. The drug release rate was found vary among the formulations depending on the compositions of polymers used. The obtained dissolution data indicated that the drug release through the microporous polymeric membrane follows fickian diffusion. Optimized formulation F5 and marketed product Aceton SR®-100 mg tablet showed similarity in drug release profile. Formulation F5 is an ideal formulation for once daily administration. From the present study, it can be concluded that the prepared matrix pellets demonstrate the potential use of SA/GPS/MCC blend for the development of controlled drug delivery systems for many water insoluble drugs.

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