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FORMULATION AND EVALUATION OF MULTIPARTICULATE DRUG DELIVERY SYSTEM

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ABSTRACT

The present work deals with the process of formulation and evaluation of pellets loaded with aceclofenac sodium (ACS) as model drug though pellitization technique by using the blend of Sodium alginate (SA) and glyceryl palmito stearate (GPS) as hydrophilic and hydrophobic carriers, along with microcrystalline cellulose (MCC) as spheronizer 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) studies and calculated sphericity factor confirms the prepared formulations were spherical in nature. The drug loaded pellets were stable and compatable, as confirmed by DSC and FTIR studies. The release of drug was controlled upto 24 h. Intestinal drug release from optimized formulation pellets was compared with the releases behavior of commercially available formulation Aceton SR®– 100 mg tablet.

KEYWORDS: Aceclofenac sodium, Pellitization, Bioavailability, Aceton SR®.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration i.e. the drug delivery system should deliver drug at a rate dictated by the needs of the body over a

specified period of treatment. Today all pharmaceutical companies call for an immediate shift to research and development emphasis. Instead of a constant research for drugs in the traditional random, new research and development strategies must be found on making the clinically established drugs to their therapeutic best. Development of novel and patentable methods of delivering these drugs by application of the concepts and techniques modifying the drug release systems has been employed.[1-3] 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. Controlled release therapeutic systems may either be passive preprogrammed or active preprogrammed or active self programmed. Most of the rate controlled delivery systems belonged to passive preprogrammed category in which the release rate is predetermined and is not influenced by the external biological environment. 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.[4] Aceclofenac sodium is 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 h) 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.[5-7] 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.[8] 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 non-toxic 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 of applications.

Preparation of pellets: Required amount (100 g batch size) of ACS, SA, GPS and MCC were passed though sieve No. 40 prior to pelletization and mixed uniformly in a planetary mixer. The buble free SLS 80 (0.3 %) solution was added dropwise to the mixture and mixed for 30 min to obtain dough mass, care should be taken in order to get lump free mass. This is because the incorporation of drug into polymer pellets requires the addition of wetting agent at an optimum concentration of aqueous solution to reduce the interfacial tension, which was

extruded using a piston extruder. The extrudates were immediately spheronized for 5 min at a rotational speed of 750 rpm and an air velocity of 1 kg/cm^2. Incorporation of drug into different ratios of SA blend affects the physical appearance of the pellets was observed. The important factor that influences the size distribution of pellets was the spheronization speed and residence time.[9] 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. The 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. The concentarion of GPS was determined by ranging from 1 to 5 % w/w of the total formulations. In the present study, optimum concentration, 5% w/w of GPS was used to produce better pellets.[10,11] 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 spheronisation by preventing phase separation, during extrusion spheronisation was observed. 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 s 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. In order to obtain optimal concentrations of pore forming agent, various concentarions of aqueous solution of SLS ranging from 0.1 to 1.0 % w/w of the total formulations were used. But 0.1 to 0.5 % of aqueous solution SLS failed

to produce required pores in the pellets. When SLS concentration is more than 0.6 % w/w, 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. The pellets were dried over night at room temperature and cured at 40 ^{o}C for 24 h in a fluid bed dryer. The dried pellets were stored in desiccator at room temperature. The formulation parameters were represented in Table 1.

Table 1. Optimization of process parameters of all ACS/SA/GPS/MCC for pelletization

Parameters	Formulation code	Parametric values	Description of pellets
ACS:SA:GPS:MCC (w/w %)	F1	30 : 30 : 01 : 39	Rod shape and brittle
	F2	30 : 25 : 02 : 43	Egg shape and brittle
	F3	30 : 20 : 03 : 47	Semi spherical and brittle
	F4	30 : 15 : 04 : 51	Spherical and brittle
	F5	30 : 10 : 05 : 55	Spherical and hard
Spheronization speed (rpm)	F5	50	Rod shape
		100	Egg shape
		150	Semi spherical
		200	Spherical
Spheronization Duration (time in minutes)	F5	3	Rod shape
		4	Egg shape
		5	Semi spherical
		6	Spherical
Yield (%)	F1	92.5	Rod shape and brittle
	F2	93.1	Egg shape and brittle
	F3	94.9	Spherical and brittle
	F4	95.5	Spherical and brittle
	F5	96.3	Spherical and hard

*Standard Deviation =3

CHARACTERIZATION

Determination of micromeritic properties of prepared pellets

All the prepared pellet formulations (F1 – F5) were subjected to micrometric analysis and the obtained data were represented in Table 2. The results of sieve analysis indicates that the prepared pellets were in the size range of 1024 to1212 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. The values of angle of repose (θ^0) 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 /cm^3), granule density (1.024 to 1.076 g/ cm^3), % 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.[12,13] 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 pellets was increased (Table 2). Additionally, pellets cured at 40^{o} C for 24 h produces pellets with good mechanical strength due to low moisture content. As the curing temperature increases (45^{o} C for 24 h), friability of the pellets found to decreases and pellets having shinked porosities was observed, due to loss of moisture content. When the pellets cured below 40^{o} C for 24 h, produced pellets were dumbbell shaped with protruding surfaces (confirmed from SEM photomicrographs) and these pellets not suitable for pharmaceutical purpose. 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 ^{o}C the sphericity values of the pellets nearer to the value 1, whereas pellets cured for 24 h at 45 ^{o}C, obtained sphericity values ranged between 1.16 -1.25 (pellets were shinked and elongated form).[14,15] The removal of residual moisture content from pellets during curing exerts an influence on the morphology of the final product.

Table 2. Micromeritic properties of ACS/SA/GPS/MCC pellets

Code	Yield (%)*	Average size (μm)*	Angle of Repose θ^{0*}	Tapped Density (g/cm^3)*	Granule density (g/cm^3)*	Carr's index (%)*	Hausner ratio (%)*	Friability (%)*
F_1	91.22 ± 0.4	1024 ± 2	27.23 ± 0.2	0.821 ± 0.03	1.024 ± 0.07	8.91 ± 0.05	1.23 ± 0.07	0.39 ± 0.05
F_2	92.80 ± 0.6	1087 ± 5	26.12 ± 0.6	0.854 ± 0.06	1.056 ± 0.05	8.65 ± 0.03	1.16 ± 0.05	0.42 ± 0.01
F_3	93.12± 0.4	1134 ± 3	25.13 ± 0.3	0.828 ± 0.04	1.054 ± 0.06	8.45 ± 0.07	1.14 ± 0.01	0.45 ± 0.06
F_4	94.45± 0.1	1189 ± 1	26.43 ± 0.5	0.873 ± 0.07	1.076 ± 0.02	8.78 ± 0.04	1.09± 0.02	0.49± 0.03
F_5	96.76± 0.3	1212 ± 4	26.23 ± 0.3	0.896 ± 0.02	1.032 ± 0.07	9.56 ± 0.02	1.12 ± 0.04	0.53 ± 0.01

*Standard deviation n = 3

Scanning electron microscopy: The scanning electron microscopy studies of pure ACS drug and the ACS/SA/GPS/MCC optimized formulation (F5) pellet was carried out to identify the morphological behavior (Figure 1). The SEM images of optimized formulation (F5) showed that pellet were spherical in nature, having a smooth surface with inward dents when they cured at 24 h at 40 ^{o}C. 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 drug particles on the surface of pellets showing uniform distribution of the drug in the walls of the pellets and also indicated the presence of minute pores over the surface. It is due to rapid diffusion of the solvent from the

walls of the pellet and there is a possibility of rupture of walls. When the pellets were cured at 45 ^{o}C for 24 h surface inward dents and shinkage were observed (collapse of the wall of the pellets), which might be due to drop in residual moisture content from pellets. The obtained sphericity factor lies in the range 1.00 - 1.06 mm, indicating that the prepared formulations were spherical in nature.

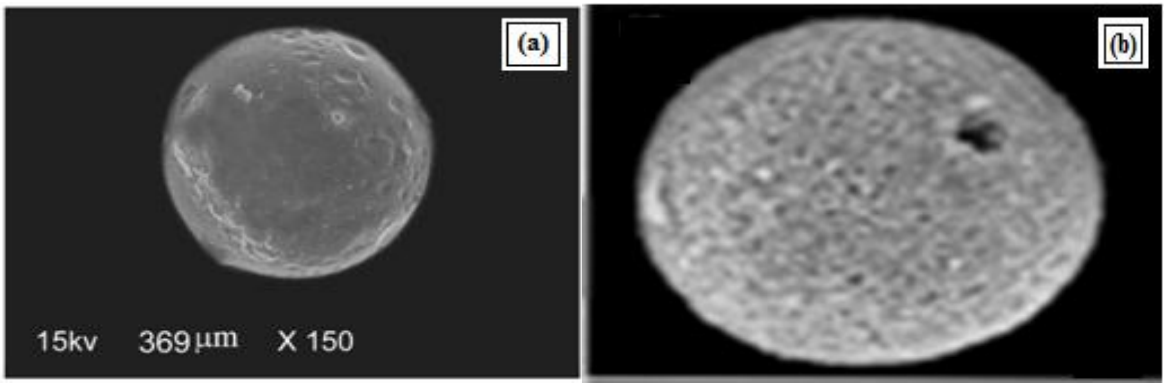

Figure 1. SEM images of (a) optimized ACS/SA/GPS/MCC formulation (F5) and (b) pore developed optimized ACS/SA/GPS/MCC formulation (F5) Pellet

Differential scanning calorimetric studies: In order to understand the compatibility of the pure ACS and prepared optimized ACS/SA/GPS/MCC formulation (F5). The studies were carried out in the temperature range ambient to 220°C in nitrogen atmosphere at a heating rate of 10°C/min. The pure ACS exhibits a sharp endothermic peak at 158.31°C. It was also observed that the presence of the endothermic peak at 158.47°C in the drug loaded optimized ACS/SA/GPS/MCC formulation (F5). This result indicates that the drug retains its identity in the prepared optimized ACS/SA/GPS/MCC formulation (F5).

Fourier Transformed Infrared (FTIR) Spectroscopic studies: The IR spectra of the pure ACS and ACS/SA/GPS/MCC optimizes formulation (F5) pellet were found to be identical and presented (Figure. 2). The IR- spectrum of the pure drug and the optimized pellet formulation ranged from 450- 4000cm^{-1} was recorded. The characteristic IR absorption bands noticed (Table 3). The spectra of the pure drug and ACS/SA/GPS/MCC optimized 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.

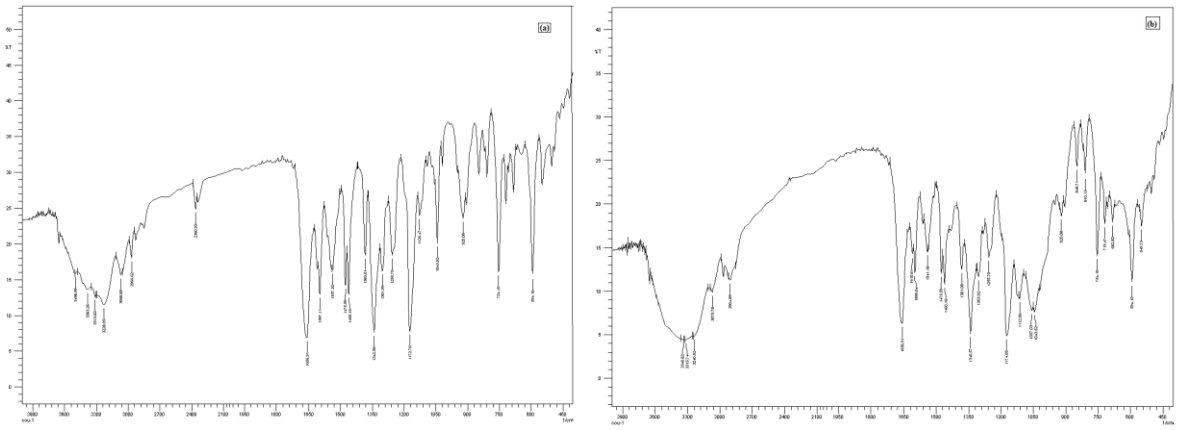

Figure 2. FT-IR spectra of (a) pure ACS and (b) optimized ACS/SA/GPS/MCC formulation (F5)

Table 3: FT-IR spectral data of pure ACS and optimized ACS/SA/GPS/MCC formulation (F5)

Group Frequency of pure drug	Peak positions in pure drug(cm-1)	Peak positions in formulation (F5) (cm-1)	Intensity range (cm-1)
Aromatic C-H stretching C-C stretching	3068.85 1600.0	3057.6 1589.4	3030-3200 1620
Aliphatic-C-H stretching C-H bending	2968.55 1467.88	2972.1 1473.66	2962-2853 1485-1445
N-H stretching	3431.8	3446.91	3400
C=C Stretching aromatic	1539.25	1587.8	1450-1600
S=O stretching	1172.76	1183.21	1050-1400

***In vitro* drug release studies:** *In vitro* release studies were carried out for the formulations in both acidic and basic media to stimulate *in vivo* conditions. Drug release from pellets in 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 hihger 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.[16-18]

Interestingly 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 penetrartion 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 ^{0}C for 24 h showed controlled drug release. Drug release upon curing at 40 ^{0}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 ^{0} 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. Figure 5, 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 (Figure 3 (a). But pellets started to looses their edges slowly by disintegration after exposed to 0.1N HCl (Figure 3 (b) for 2 h. When pellets exposed to phosphate buffer pH 7.4 (after 2h) (Figure 5 (c), 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. Loose surface crystal (LSC) study observation has clearly indicates the pellets with increasing concentrations of SA, results on LSC decreased significantly.[19] 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. 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. Experimental 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. 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 Figure 4. 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 4. 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 less amount 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 though the pores formed in the pellets membrane. 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/). Interstingly drug content increases with increased in pellets size (1024 to1212 μm).[20] This might be due to increased relative surface area of the pellets, leads to more drug content.

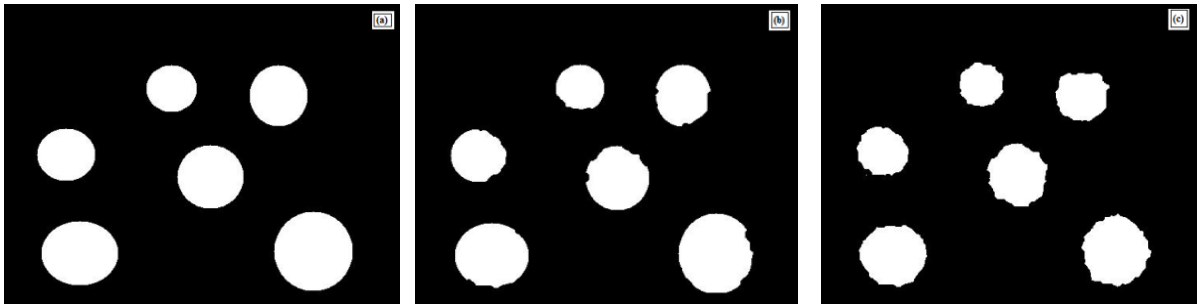

Figure 3. Microscopic photographs of optimized formulation (F5) pellets (a) before exposure, (b) 2 h exposure to 0.1N HCl and (c) 4 h exposure to pH 7.2 phosphate buffer

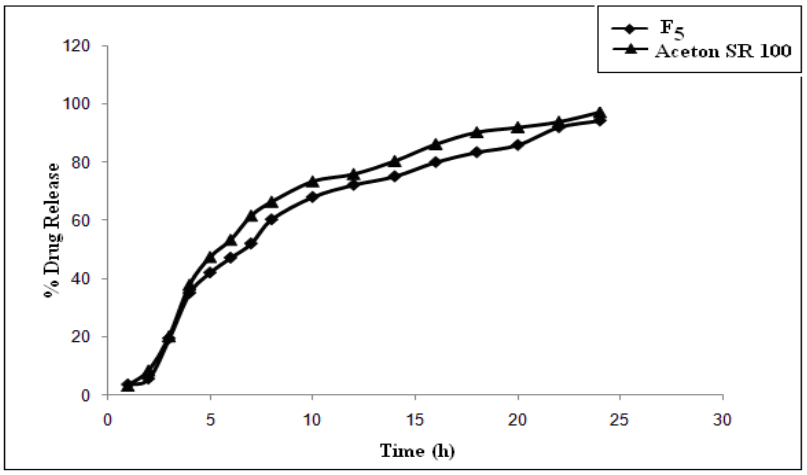

Figure 4. Percent drug release profiles of optimized ACS pellet formulation (F5) and Aceton SR® 100 mg tablet in the intestinal environment.

Table 4. Diffusivity data for SA/ GPS and MCC

Formulation	D_1 [a] x 10^9(cm^2/s)	D_2 [a] x 10^9(cm^2/s)
Trial 1 (Without GPS)	1.43	1.32
F1	0.48	0.38
F2	0.53	0.50
F3	0.64	0.62
F4	0.73	0.69
F5	0.94	0.88

[a] Standard Deviation n = 3,

Stability studies of pellets: After determining the drug content, the optimized drug contain pellets were charged for the accelerated stability studies according ICH guidelines (Table 5). 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 ^{0}C and 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. It is evident from the table that, formulations F5 exhibited good stability during investigation period, which indicates the drug was in stable form.

Table 5. Stability studies of optimized ACS/SA/GPS/ MCC formulation (F5) pellets

Stability condition	Sampling (in days)	Drug content (in mg) Mean ± SD*
40ºC/75% RH	0	97.42 ± 0.21
	15	97.40 ± 1.33
	45	97.99 ± 0.82
	90	97.38 ± 0.25

*Standard Deviation, n=3

CONCLUSION

The (30: 10: 05: 55) ACS/SA/GPS/MCC polymer/drug blend emerged as the optimized formulation (F5). The MCC possess physical properties and behaviour suitable to prepare gastro resistant, biocompatible, biodegradable porous pellets to release the entrapped drug in the GI tract were well within the standard Indian pharmacopeia limits. FT-IR studies, reveals that similar characteristic peaks appear with slight differences for the pure ACS drug and (F5) formulation pellets. The DSC study reveals the pure ACS drug and for optimized (F5) formulation pellets shows no significant shift in the endothermic melting peak confirming the presence of drug in the prepared formulation and there is no interaction between drug and polymers. The SEM studies indicates the obtained optimized (F5) formulation pellets exhibited good spherical nature without any dents and free from surface irregularities. The micropores were well developed during the sustained release process. Drug content study results inferred that there was a proper and uniform distribution of drug within formulated pellets. The percentage encapsulation efficiency study results have clearly showed that the drug loading is optimum for (F5) formulation pellets. 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 The SLS, has successfully emerged as micropore developer on the surface of the pellets. The *in vitro* drug release studies reveal that, the release of drug from the optimized (F5) pellets was found to be diffusion controlled and the process followed first order kinetics and drug ACS release mechanism though the microporous polymeric membrane follows Fickian type of diffusion. The stability studies results signifies that there was no change in drug content after 90 days of investigation period hence they were stable and potent. The drug release was controlled from

ACS pellets controls than the commercially available product Aceton SR®– 100 mg tablet. Optimized ACS/SA/GPS/MCC blend formulation (F5) pellets has clearly proves as an ideal dosage form for once daily administration for the development of controlled drug delivery systems for many water insoluble drugs.

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