Original Article

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New Approach for Sustained Release Dosage Form Design: Aceclofenac

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Abstract

In pharmaceutical dosage form preparation, eggshell powder has been explored for the new application as pharmaceutical excipient. So, our present study was undertaken to develop sustained release (SR) matrix tablets of aceclofenac using eggshell powder as newly investigated pharmaceutical excipient. Two different eggshell powders were used. These included ethanol treated and chloroform treated eggshell powders. The treated samples were prepared by surface modification using 1.0 % w/v stearic acid in solvent namely deionized water, 95 % ethanol and chloroform. Different formulations (F1-F6) were prepared by wet granulation method along with HPMC, treated eggshell powder as release retardant polymer and other ingredients. Dissolution studies of six aceclofenac formulations in pH 6.8 phosphate buffer were performed using USP Dissolution Apparatus II. The evaluation involves two stages-the physical properties studies of tablets and *in vitro* release kinetics assessment. The release kinetics was analyzed using Zero order and Higuchi's equation. Significant differences were found among the drug release profile from different levels of using HPMC and treated eggshell. From Higuchi model plot it was found that chloroform treated eggshell powder containing formulation (F-5) shows most amendable sustain release over 24 hours than ethanol treated eggshell powder containing formulation (F-3). The *in-vitro* release studies revealed that F-5 can be taken as an ideal or optimized formulation of sustained release tablets for 24 hours release as it fulfills all the requirements for sustained release tablet. Sustained release of the drug may be due to hydrophobic nature of the treated eggshell powders and the degree of hydrophobicity of the treated eggshell powders depends on the type of solvent used in surface modification process. That's why chloroform treated eggshell powder showed greater sustained release profile. The results obtained from this study suggest using treated eggshell powder as an inexpensive pharmaceutical excipient instead of commercial expensive release retardant polymer to control the drug release from the tablet. Furthermore, this finding will be useful in the development of biomaterials from eggshell waste by recommending the new dimension of eggshell powder in pharmaceutical industry.

Keyword: Aceclofenac, Eggshell, Higuchi's equation, Sustained release.

1. INTRODUCTION

The basic goal of therapy is to attain a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in completing this goal. Sustained release dosage forms are intended to deliver the drug at a controlled and predetermined rate, thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time and therefore reducing the frequency of dosing and improving patient compliance[1].

Non-steroidal anti-inflammatory drugs

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(NSAIDs) are measured to be the first-line drugs in the treatment of ankylosing spondylitis, rheumatoid arthritis and osteoarthritis. Aceclofenac is one of the emerging NSAID for arthritis treatment. It is a newer derivative of diclofenac and has less gastrointestinal difficulties. The short biological half-life (about 4 h) and dosing frequency more than one per day make aceclofenac an ideal candidate for sustained release. To lessen the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of aceclofenac is desirable[2-5]. For sustained release systems, the oral route of drug administration has received the most attention as it is natural, uncomplicated, convenient and safer route[6].

There are several types of release retardant (e.g., methylcellulose, sodium carboxymethylcellulose, polyvinyl chloride, etc.) that are used in formulation of aceclofenac sustained release dosage form[7]. Eggshell powder can be an interesting release retardant in developing oral sustained release formulation. The drug release from this matrice can be controlled through its physical properties. Many studies have found that eggshells are used as a stabilizing material for refining soil properties[8], as coating pigments for ink-jet printing paper[9], as food additive[10] and as a source of calcium in animal and human nutrition[11-13]. The chemical compositions of eggshell are calcium carbonate (94%), magnesium carbonate (1%), calcium phosphate (1%) and organic matter (4%)[14]. As the major component of the eggshell is calcium carbonate, it can be used to substitute calcium carbonate, which is used as pharmaceutical excipient in solid dosage forms. In addition, calcium carbonate from eggshell has an advantage for not containing toxic elements such as aluminum, cadmium and mercury[15].

Depending on such extensive uses and advantages of eggshell, we have tried to develop aceclofenac sustained release dosage form using eggshell powder as release retardant in this study. We believe that this developed formulation would help to transform the waste eggshells into a valuable item providing economical assistances to the egg processing industry and help to overcome the high disposal costs and environmental concerns as well.

2. MATERIALS AND METHODS

2.1 Materials

All the ingredients were provided from the Department of Pharmacy, Dhaka International University including active ingredient- Aceclofenac and other excipient like HPMC, Povidone-K30, Mg stearate, Talc, Starch. Eggshells were collected from home and hotels. Solvents and all other chemicals were of analytical grade.

2.2 Eggshell particles preparation

The eggshell membrane was removed and the eggshell was washed thoroughly with tap water. Then the eggshell was boiled in deionized water for 30 minutes. It was dried in hot air oven at 80˚C for 2 h. The dried eggshell was crushed and ground using porcelain mortar and pestle. The eggshell powder which passed 200 mesh sieves was used in the study.

2.3 Treated eggshell particles preparation

20 g of the eggshell particles was treated with 20 mL of 1.0 % w/v stearic acid solution in three different solvents, i.e., water, 95% ethanol or chloroform in glass mortar. In case of water, boiling water was used and the sample was dried in an oven at 45 ˚C overnight. In cases of ethanol and chloroform, the experiments were carried out at room temperature and the samples were left overnight at room temperature.

2.4 Preparation of Matrix Tablet

Matrix tablets, aceclofenac each containing 760 mg were prepared by direct compression. The active ingredient and other excipients were accurately weighted for thirty five tablets according to the formulations. Properly weighed ingredients were blended in a laboratory designed small drum blender. Particular attention has been given to ensure through mixing and phase homogenization. Finally the resultant blend was compressed

using a pilot plant tablet machine having fitted with cylindrical shape punch and die[16]. The length and width of tablets depends on the die and punches selected for making the tablets. Thus the final morphology of tablet under optical microscope after formulation was found round cylindrical shaped.

2.5 Physical evaluation of Tablet

All prepared matrix tablets were evaluated for uniformity of weight and uniform morphological properties. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester. Diameter and thickness were measured by Vernier caliper[17].

2.6 In-Vitro Release Studies

Dissolution Study

Dissolution medium was prepared according to USP method. It was prepared by dissolving 0.66g of di-sodium hydrogen phosphate (1M Na_2HPO4) into 463mL of water and 0.847g of sodium di-hydrogen phosphate (1M NaH_2PO4) into 537mL of water, then two solutions was mixed together. The pH was adjusted to 6.8 with either 0.1 M sodium hydroxide or 0.1 M hydrochloric acid as required**.** The *in vitro* dissolution studies were performed using USP type-II dissolution apparatus (Rotating Paddle method) at 50 rpm. The dissolution medium was maintained at 37°C ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals which replaced by equivalent amount of buffer solution. The drug content was determined by UV-visible spectrophotometer (SHIMADZU UV-1240 spectrophotometer) at 276 nm. The release studies were conducted in triplicate.

2.7 Analysis of Release Data

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), and Higuchi (cumulative percentage of drug release versus square root of time) equation models.

3. RESULTS AND DISCUSSIONS

In this present study, aceclofenac was used as a model drug. Figure 1 embodies the standard curve of aceclofenac. The proposed formulations for sustained release aceclofenac matrix tablet were mentioned in table 1. Table 2 describes the physical parameters of aceclofenac from proposed formulations. From table 2, it was found that all the batches showed uniform thickness, length and widths. The average percentage deviation of ten tablets of each formulation was less than 5% and hence all formulations passed the test for uniformity of weight as per official requirements. The hardness of all the formulations is within the range of limit (4.5±0.6kg). The use of Povidone K-30 & HPMC has smoothed the compression of the tablets and made it possible to impart proper hardness settings. It is possible to have better control in a larger production control. The percentage of friability of the tablets of all the formulations also within the range (<1%). So, all the tablet formulations showed satisfactory pharmacopoeial properties. Table 3 states the regression value of developed formulations fitted with zero and Higuchi equations. Zero-order release model of aceclofenac sustained release formulations is illustrated in figure 2. Figure 3 defines the Higuchi release model of aceclofenac sustained release formulations. The time required for 25%, 50% and 75% drug release according to Higuchi equation is stated in table 4. The dissolution data of all formulations were tailored into two mathematical models (zero-order, Higuchi model) to know which mathematical model will best fit for the drug release profile. Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. It is clearly specified that, the formulations did not follow a zero-order release pattern because the regression value for all formulations did not show high linearity. When the data where plotted according to a Higuchi equation, the formulations F-1, F-2, F-3,F-4,F-5 and F-6 showed a fair linearity, with regression values 0.9514, 0.9838, 0.9743, 0.9772, 0.9536 and 0.9642 respectively. Time required for 25%, 50% and

75% of drug release was corrected using linear equation of Higuchi plot. From this study, it was observed that chloroform treated eggshell particle comprising formulation (F-5) have more constant release action than ethanol treated eggshell powder (F-3). All other formulations revealed fast release profile. It was also observed that F-5 required more than 18.23 hours for 75% release. So, it can be resolved that 24 hours would be required for 100% release. The possible reason for release extension is the hydrophobic nature of the treated eggshell powders and the type of solvent used in surface modification process[16]. Due to the effect of stirring provided to the dissolution medium, some attrition of the coating layer or pore formation on coating layer may occur. This leads to a limited entry of dissolution medium into the core. This results in immediate release of the drug. Again, dissociated stearic acid in the acid medium formed calcium stearate on the surface of the particle. This may prevent or retard wetting of the tablet surface which in turn results in the delay release of the drug[16]. On the other hand, the treated tablets surface is hydrophobic in nature. The more hydrophobicity in nature the more extended time to release drug. As the hydrophobicity of chloroform is greater than ethanol, so chloroform treated eggshell powder should have more extended release action.

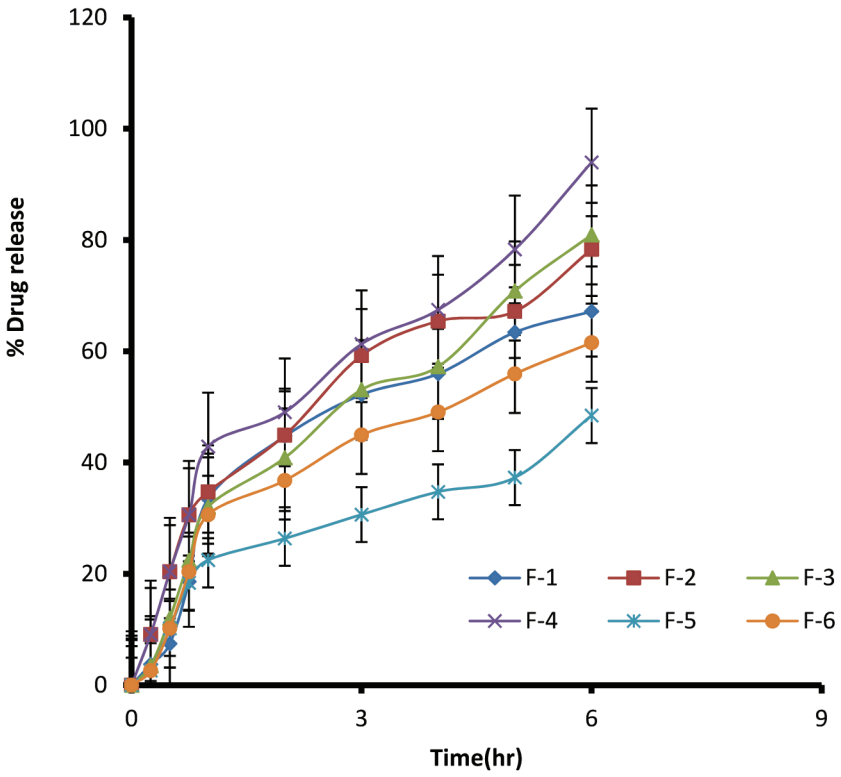

Figure 1. Zero-Order release model of aceclofenac sustained release formulations

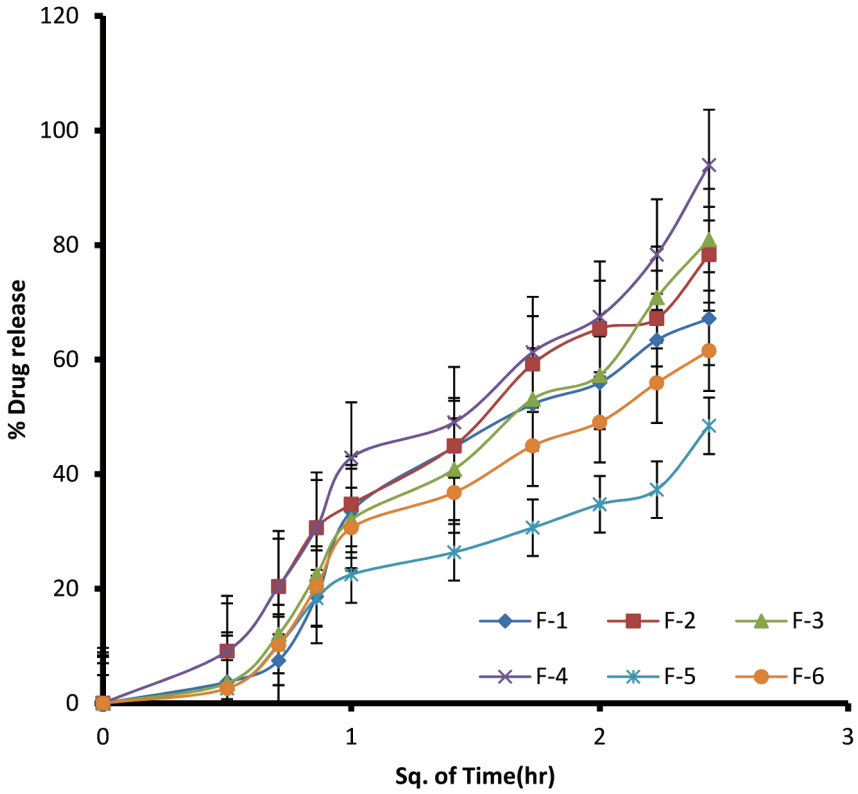

Figure 2. Higuchi release model of aceclofenac sustained release formulations

Table 1. Proposed formulations for sustained release aceclofenac matrix tablet

Ingredients		Amount (mg)					
		F-1	F-2	F-3	F-4	F-5	F-6
Aceclofenac		250	250	250	250	250	250
HPMC		0	150	75	0	75	0
Eggshell powder	Ethanol Treated	150	0	75	0	0	75
	Chloroform Treated	0	0	0	150	75	75
Lactose		150	150	150	150	150	150
Mg stearate		5	5	5	5	5	5
Talc		5	5	5	5	5	5
Povidone-k30		200	200	200	200	200	200
Total		760	760	760	760	760	760

Table 2. Physical parameters of aceclofenac from proposed formulation

Code	Thickness (mm) ±SEM	Length (mm) ±SEM	Width (mm) ±SEM	Hardness (Kg/f) ±SEM	Friability (%)
F-1	9.28±0.23	17.6±0.41	5.05±0.44	10±1.5	0.08
F-2	9.30±0.26	17.5±0.52	5.03±0.53	6.8±2	0.13
F-3	9.31±0.19	17.49±0.59	5.04±0.65	7±0.5	0.46
F-4	9.0±0.22	17.55±0.37	5.06±0.44	5±1.5	0.36
F-5	8.72±O.33	17.5±0.61	5.05±0.57	6.75±2.2	0.32
F-6	8.29±0.36	17.48±0.49	5.04±0.68	7±1..25	0.48

Table 3. The regression value of developed formulations fitted with zero and Higuchi equations

Formulation	Zero-order regression coefficient (r^2)	Higuchi equation regression coefficient (r^2)
F-1	0.8759	0.9514
F-2	0.8982	0.9838
F-3	0.9445	0.9743
F-4	0.9222	0.9772
F-5	0.885	0.9536
F-6	0.8908	0.9642

Table 4. Time required for 25%, 50% and 75% drug release according to Higuchi Equation

Code	$t_{25\%}$	$t_{50\%}$	$t_{75\%}$
F-1	4.92	9.83	14.75
F-2	5.5	11	16.5
F-3	4.0	8.0	12.0
F-4	3.15	6.30	10.5
F-5	6.08	12.15	18.23
F-6	7.15	14.30	21.5

4. Conclusion

Depending on the results of our present study, it can be ended that eggshell powder has unique quality to hold drug firmly through sustained dosage form. The chloroform treated eggshell powder should be the stronger rate-retarding agents in aceclofenac sustained release dosage form. This formulation can promote desired controlled drug release upon hydration, swelling and gel formation when interact with gastrointestinal fluid. However, further analysis is required to establish *in vivo-in vitro* correlation to reveal the accurate pattern of drug release in *in vivo* environment as well as any toxic effect of this formulation since the process for synthesis of eggshell material need to be use some organic solvents.

COMPETING INTERESTS

We declare that we have no competing of interest.

AUTHORS' CONTRIBUTION

MAH- participated in experiments, study design, manuscript preparation. **MFM**-carried out the study design, participated in experiments, manuscript preparation, statistical analysis. **MH, SKA**-Supervising and directing the project. **MMB**-checked the grammatical mistakes and corrected the final manuscript. **MMB, MR**- participated in experiments and statistical analysis. All authors read and approved the final version of the manuscript.

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