DESIGN AND EVALUATION OF SMART MUCOADHESIVE KETOPROFEN LOADED BIO-MICRODWARFS

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Summary

The aim of our research work was to isolate a novel bio-material from fruit pulp of *Artocarpus heterophyllus* and to evaluate its muco-retardability by formulating bio-microdwarfs using ketoprofen as a model drug. The bio-material was isolated from fruit pulp of *Artocarpus heterophyllus* by our earlier published method. It was subjected for various physicochemical parameters like color, colour changing point, chemical tests, spectral study and mucoretentivity studies by using M.S. apparatus, Park and Robinson method, rotating cylinder method and shear stress method, which was compared to standard polymers like sodium CMC and HPMC. Six ketoprofen loaded bio-microdwarfs(FA1-FA6) were prepared using various ratios(1:0.25, 1:0.5, 1:0.75, 1:1, 1:1.25, 1:2) of bio-material by solvent evaporation method. The formulated bio-dwarfs were subjected for various evaluation parameters like particle size, shape, content uniformity, ex-vivo mucoadhesivity, *in-vitro* release studies. Our experimental research showed that the isolated bio-material possesses good mucoadhesivity. The formulated bio-microdwarfs showed uniform particle Size, shape with promising mucoadhesivity. The bio-microdwarfs showed a particle size in the range 137-158µm and a content uniformity of 61-67%. The formulation FA4(1:1) was found to be the best formulation as it showed extended release upto 8 hours, having t80% of more than 400mins and with a content uniformity of 67.8%. A smart conclusion was drawn that the isolated bio-polymeric material can serve as a good retarding agent for the formulation of various drug loaded of mucoadhesive bio-microdwarfs.

Key words: micro dwarfs, ketoprofen, *Artocarpus heterophyllus*, mucoadhesive

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Introduction

Ketoprofen, (RS)2-(3-benzoylphenyl)-propionic acid (chemical formula $C_{16}H_{14}O_3$) is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. [1] Jackfruit (*Artocaropus Heterophyllus)* belongs to the family moraceae, it contains morin, carotenoids, provitamin A. It is used medicinally as a laxative, tonic and demulcent. Jackfruit pulp contains morin and a crystalline constituent, cyanomaclurin, probably isomeric with catechins. It is a Good source of provitamin A, carotenoids.

Materials and Methods

The drug ketoprofen was obtained as a gift sample from ranbaxy paonta sahib, India. Jackfruit was procured from the local market. All other reagents used were of highest purity and analytical grade. Double distilled water water was used throughout the experimental work.

Bio-material extraction

The bio-material was isolated from the fruits of artocarpus heetrophyllus from our previously published method. The isolated bio-material was subjected for physico-chemical characterization and spectral analysis.[2]

Mucoadhesivity screening of the isolated bio-material:

The bio-material was evaluated for the mucoadhesivity by the modified shear stress apparatus[2]. In this method the bio-material solutions ranging from 1% to 5% were prepared and spread on a fixed glass plate on a board. Above it was kept another glasss plate(movable) to which was attached a string connected to a empty box in which weight could be added. This box was placed on a digital weight balance. The mucoadhesivity was determined at different intervals and compared with sodium CMC 1% solution.

Formulation of microparticles:

The emulsion-solvent evaporation can be used to prepare the microparticles of ketoprofen. The method employed is widely used in micro particulate preparation for controlled release of many drugs. In this method basically the polymer(bio-material) is dissolved in a suitable solvent (in which the drug also shows perfect solubility) to get a clear solution. The drug dissolved into this polymer(bio-material) solution. The resultant solution added slowly into the liquid paraffin solvent having 1% span-80 (as an emulsifier) with continuous stirring at 900 rpm with a mechanical stirrer for 2 hrs. After the volatile solvent gets evaporate fully, the microparticles were formed then washed it three times with n-hexane to make them oil-free and collected by vacuum filtration with full removal of the solvent, air dried and stored in the desiccator for further use.

Evaluation of microparticles:

Particle size determination

Measurements of the particles size distributions and mean diameters of the microparticles were carried out with an optical microscope. Fifty randomly chosen microparticles were taken to measure their individual shape and size. Triplicate readings were taken and standard deviation calculated.

Determination of drug entrapments efficiency, drug loading, and yield:

Microparticles (25 mg) were suspended in 25 ml of methanol. After 24 hrs, the solution filtered and the filtrate was analyzed for drug content; this filtrate was diluted up to appropriate dilution; and for the determination of drug entrapment efficiency, the following formulas were used:

Encapsulation Efficiency (%) =(Actual drug content × 100)/ Theoretical drug content

Yield (%)=(Weight of Microparticles× 100) / Total expected weight of drug and polymer

Micromeritic properties:

Angle of repose Angle of repose of different formulations was measured according to fixed funnel standing method(n = 3)
$\theta = \tan^{-1} h / r$ where θ is the angle of repose, r is the radius, and h is the height.

***Ex-vivo* mucoadhesion study: determination of retention time:[2]**

The *ex-vivo* muciretenhtion time was found by the M.S. apparatus method [2]and the rotating cylinder method. The goat intestinal mucosa was used to study the mucoadhesion retention time by the rotating cylinder method. The goat intestinal mucosa was fixed to a rotating basket of the USP dissolution apparatus. The reservoir filled with intestinal simulated buffer and temperatute maintained a 37±0.5˚C. The dissolution apparatus(basket) was rotated at 50 rpm and time for the dislodgement of the microparticles from the intestinal mucosa was recorded as the retention time. The triplicate readings were performed and standard deviation applied.

***In-vitro* dissolution analysis:**

In-vitro dissolution studies were carried out on the microsphere at 37°C ± (0.5°C) at 50 rpm with USP dissolution apparatus II; 100-mg ketoprofen microparticles was place into the dissolution apparatus. The *in vitro* dissolution studies were performed, taking 0.1 N HCl ≈ gastric medium. The study was then performed up to 10 hrs. The sample (5 ml) was withdrawn at each 0.5 hour interval and replaced with the same volume of test medium and the withdrawn samples were diluted if required and then estimated for concentration spectrophotometrically.

Application of kinetic models

The dissolution data of all controlled-release microparticles and control formulation was fitted to kinetics models i.e., zero order, first order, Higuchi, and Korsmeyer–Peppas to find out drug release pattern and mechanism.

Results and Discussions

The ketoprofen loaded bio microdwarfs were prepared using isolated bio-material from the unripened fruit pulp of *Artocarpus heterophyllus.* the isolated bio-material was screened for mucoadhesivity and it was found to be comparable to the mucoadhesive strength of sodium CMC at a concentration of 3%-5%.

The six ratios of the bio-microdwarfs were prepared and evaluated for particle size, drug loading, entrapment efficacy, angle of repose, retention time and *in-vitro* release study. The particle size was found to be in the range137.7±0.46 to 203.4±0.85, entrapment efficacy in the range 61.4±1.65 to 73.2±1.68. the formulations were free flowing as indicated by the angle of repose. The formulation FA4 was found to be the best formulation on the basis of evaluation parameters, retention time of more than 6 hours with highest entrapment efficacy of 73.2±1.68, % yield of 91.3±0.98 and sustained release of more than 10 hours. The in-vitro release study indicates fickian release profile, diffusion controlled.

Table no. 1: Formulations

S.No.	Formulation	FA1	FA2	FA3	FA4	FA5	FA6
1.	Drug(mg)	50	50	50	50	50	50
2.	Bio-material(mg)	12.5	25	50	62.5	75	100

Table no. 2: Evaluation Parameters

FORMULATION	**FA1**	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**
PARTICLE SIZE(µm)	**137.7±0.46**	**145.3±1.2**	**156.3±0.94**	**173.4±1.43**	**198.3±0.56**	**203.4±0.85**
% YIELD	**83.24±2.1**	**81.3±1.5**	**85.3±1.5**	**91.3±0.98**	**87.7±2.1**	**89.3±2.5**
ENTRAPPMENT EFFICACY	**64.5±0.93**	**67.8±1.7**	**61.4±1.65**	**73.2±1.68**	**69.5±2.1**	**68.7±0.83**
ANGLE OF REPOSE	**22.3±0.4**	**21.5±0.6**	**23.6±0.2**	**24.5±0.7**	**23.1±0.4**	**22.6±0.89**
MUCOADHESION RETENTION TIME(HOURS)	**4.6±0.32**	**4.9±0.25**	**5.6±0.14**	**6.4±0.36**	**6.6±0.27**	**6.8±0.37**

Table no. 3 release kinetics

Formulation (Drug:Polymer)	Zero-Order R^2 VALUE	First-Order R^2 VALUE	Higuchi Model R^2 VALUE	Korsemeyer-Peppas Model R^2 VALUE	Mechanism of drug release
FA1	**0.958**	0.946	0.881	0.788	Fickian
FA2	**0.960**	0.970	0.970	0.930	Fickian
FA3	**0.969**	0.965	0.915	0.830	Fickian
FA4	**0.989**	0.986	0.984	0.958	Fickian
FA5	**0.976**	**0.974**	**0.982**	**0.985**	Fickian
FA6	**0.983**	**0.987**	**0.989**	**0.964**	Fickian

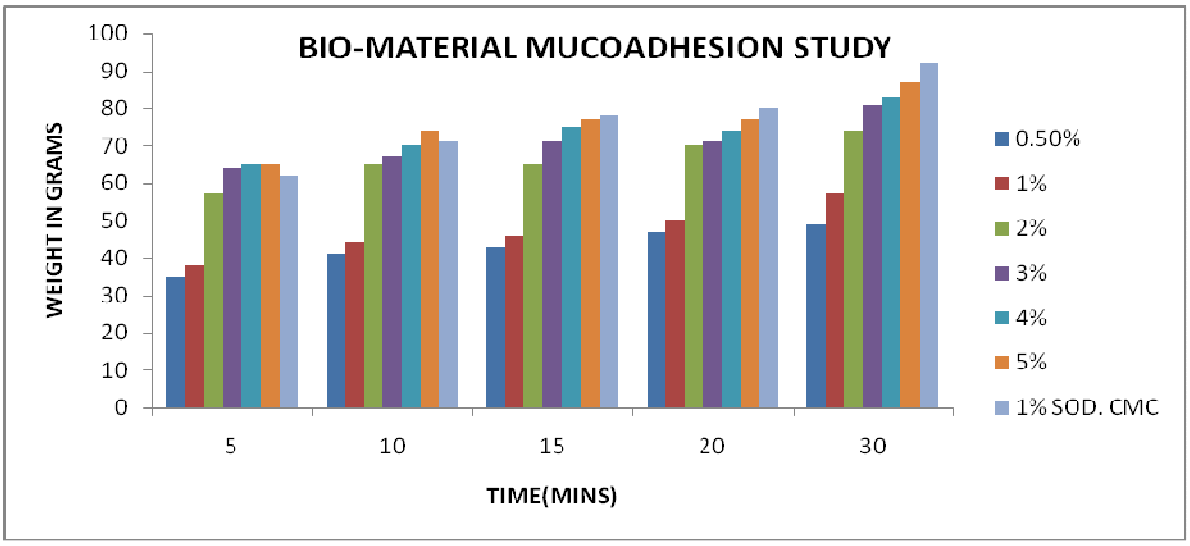

Fig. no. 1 jackfruit bio-material shear stress study: mucoadhesivity

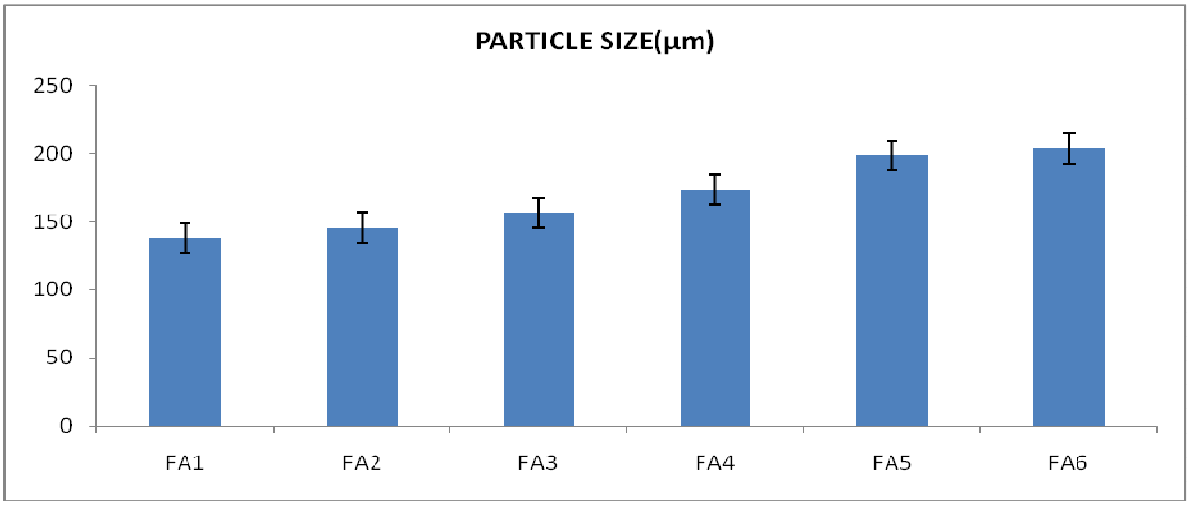

FIG. NO.2 particle size of bio-micro dwarfs of ketoprofen

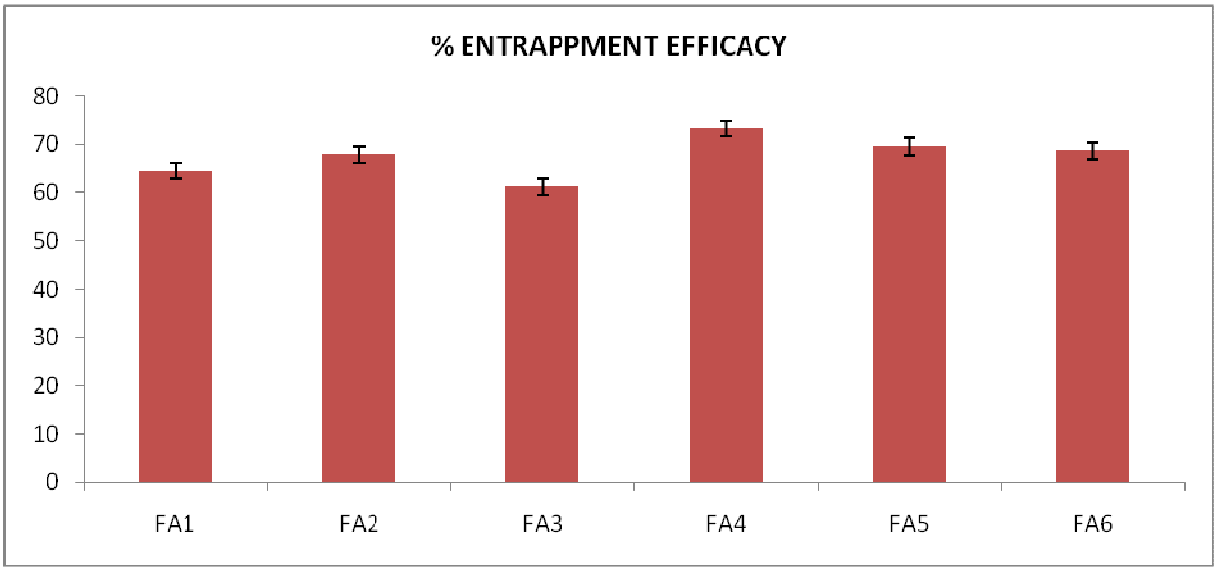

Fig. no.3 % entrapment efficacy of bio-micro dwarfs of ketoprofen

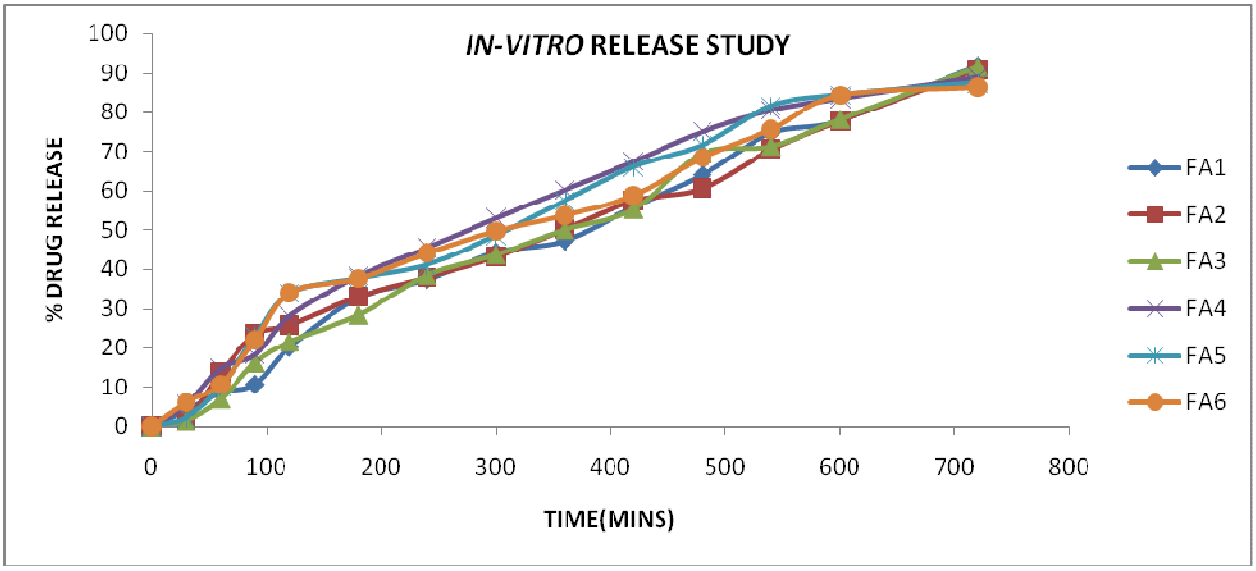

Fig. no. 4 in-vitro release profile of formulated bio-micro dwarfs of ketoprofen

Conclusion

It can be concluded that the isolated bio-material can serve as a potential retardant for the formulation of various sustained, controlled release formulations. Further it can be said that the bio-material possess excellent mucoadhesivity and hence can be used for the formulation of mucoadhesive dosage forms.

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