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Formulation and evaluation of atorvastatin loaded extended release tablets

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ABSTRACT

The aim of our research work was to formulate and evaluate sustained release tablets of atorvastatin using the bio-material as a novel bio-binder for the formulation of tablets. The bio-material was isolated from the unripe fruit pulp of Artocarpus heterophyllus by simplified economic process. It was subjected for various physicochemical parameters like color, colour changing point, chemical tests, IR spectral study. Ibuprofen sustained release tablets were prepared by using various formulation additives. Three atorvastatin loaded formulations(FA1-FA3) were prepared by using varying polymer ratios of 1:1, 1:3, 1:5 and other excipients like starch, talc, lactose. The formulations were evaluated for hardness, friability, weight variation, disintegration and in-vitro release study. On the basis of evaluation parameters formulation FA3 was found to be the best as It showed a t50% of 400 mins and t80% of more than 10 hours with weight variation of 3.8%, friability of 1.2%, hardness of 5 kg/cm^{2}and disintegration time of around 12 mins. A smart conclusion was drawn that the bio-material can serve as a potential agent for formulating various sustained release formulations for the treatment of various chronic ailments along with the advantages of being non-toxic, biodegradable and free from any adverse effects.

Key Words: *Artocaropus Heterophyllus*, Atorvastatin, Bio-Material, Sustained Release

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INTRODUCTION

Jackfruit (*Artocaropus Heterophyllus)* belongs to the family moraceae, it contains morin, carotenoids, provitamin A. It is used medicinally as a laxative, tonic and demulcent. The drug atorvastatin is an HMG-Coenzyme inhibitor and is used for the treatment of hyperlipidimea i.e. elevated cholesterol levels in the body. It is generally administered once daily, the aim of our experiment is to formulate a ovel bio-polymeric based sustained release tablet of atorvastatin for once daily dosing. Jackfruit pulp contains morin and a crystalline constituent, cyanomaclurin, probably isomeric with catechins. It is a Good source of provitamin A carotenoids. It is also composed of a new flavonone, a new prenylfalvone, a novel phenolic compound, heterophylol and nine known flavonoids. Ripe fruit is used as demulcent, nutritive, laxative. Pulp or flesh surrounding the seed is aromatic, cooling and tonic. It is also used in Diarrhea, fever and asthma. (1-2) Atorvastatin, is a member of the drug class known as statins, used for lowering blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body. Atorvastatin undergoes rapid oral absorption, with an approximate time to maximum plasma concentration (T_{max}) of 1–2 hours. The absolute bioavailability of the drug is approximately 14%; however, the systemic availability for HMG-CoA reductase activity is approximately 30%. Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low

systemic availability. Due to its rapid clearance from the body a sustained release product is required for it to exert its pharmacological effect. In the current research project we aim at formlulating a sustained release tablet of atorvastatin using a bio-binder from the fruit pulp of *Artocarpus heterophyllus*

MATERIALS AND METHODS

The drug atorvastatin 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 hetrophyllus* from our previously published method. The isolated bio-material was subjected for physico-chemical characterization and spectral analysis.(2)

Formulation of atorvastatin sustained release tablets: (table no. 1)
The tablets were prepared by Accurately weighing the drug, bio-material, starch, lactose, talc & magnesium stearate. These were mixed in a pestle mortar by geometric progression. Solutions of varying strength of the bio-polymer were prepared(1:1,1:3,1:5) and used as a binder solution. A damp, sticky mass was prepared and the granules were prepared by passing through sieve no. 22. The granules were dried in oven at 45°C for 15 mins. Talc and magnesium stearate was added to enhance the flow properties. The granules were than compressed in the tablet punching machine to get the tablets. The tablets were evaluated for the various evaluation parameters.

Table no. 1: Formulations

S.No.	Formulation	FA1	FA2	FA3
1.	atorvastatin(mg)	10	10	10
2.	Bio-polymer(mg)	30	90	150
3.	starch (mg)	50	50	50
4.	Magnesium stearate (mg)	5	5	5
5.	Talc (mg)	5	5	5
6.	Lactose(mg) q.s. to	300	300	300

EVALUATION PARAMETERS: (table no. 2a, 2b)
Characterization of Granules(3-7)
Prior to compression, granules were evaluated for their characteristic parameters. Angle of repose was determined by funnel method. Bulk density and tapped density were determined by cylinder method, and Carr's index (CI) was calculated using the following equation.

$$CI = (TD-BD)*100/TD$$

where, TD is the tap density and BD is the bulk density.

The tablets were evaluated for the following parameters:
- Hardness
- Weight variation
- Friability
- Disintegration time
- In-vitro release study

Hardness: The hardness was evaluated by the common laboratory hardness tester. The triplicate of three observations was performed and standard deviation applied to the results. (fig. no.3)(8-10)

Weight variation: The weight variation study was performed by weighing individually ten tablets and finding the average weight. The deviation of the weight of the tablets from the average weight was determined as the weight variation. The triplicate of three observations was performed and standard deviation applied to the results. (fig. no. 4)(11,12)

Friability: The Roche friabilator was used to determine the friability of the tablets. The triplicate of three observations was performed and standard deviation applied to the results. (fig. no. 5)(8-10)

Disintegration time: The disintigartion apparatus was used to determine the disintegration time of the tablets. The triplicate of three observations was performed and standard deviation applied to the results. (fig. no. 6)(8-10)

***In-vitro* release study:** The in-vitro release of the tablets was performed in USP dissolution apparatus type II for 10 hrs in ph 1.2 for the first two hours and in ph 7.4 for the next 8 hours. (1-10)

Kinetic Analysis of Dissolution Data

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation. These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems

$$\text{Log}(Mt/Mf) = \text{Log } k + n \text{ Log } t$$

where, M_t is the amount of drug release at time t; M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release.(table no.3)(11-12)

Table no. 2a: Evaluation Parameters of atorvastatin granules

Evaluation parameter	FA1	FA2	FA3
Angle of repose(°)	25.34±1.2	24.37±0.65	27.64±1.1
Bulk density(g/mL)	0.64	0.43	0.57
Tapped density(g/mL)	0.75	0.58	0.69
Carr's index	17.185	25.86	17.39

Table no. 2b: Evaluation Parameters of atorvastatin tablets

Evaluation parameter	FA1	FA2	FA3
Hardness (kg/cm^2)	4	5	5
Friability	1.3%±0.045	1.2%±0.075	1.82%±0.057
Weight variation	4.5%±0.36	3.8%±0.24	4.4%±0.42
Disintigration time(mins)	29mins±3.5 mins	33 mins± 2.4 mins	37 mins± 2.8 mins

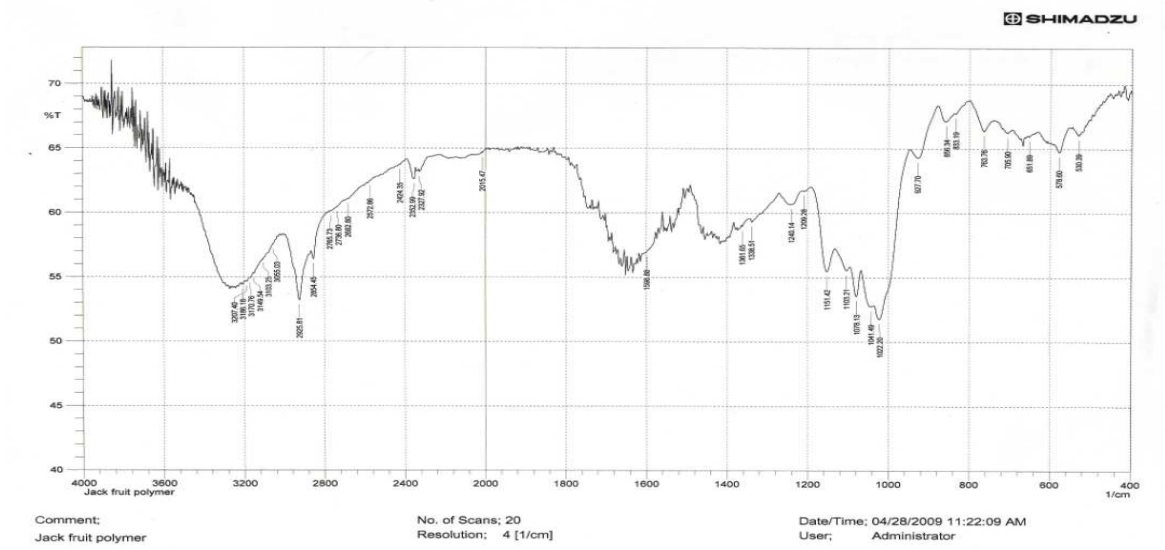

Fig. No. 1 Infra red spectra of the bio-material

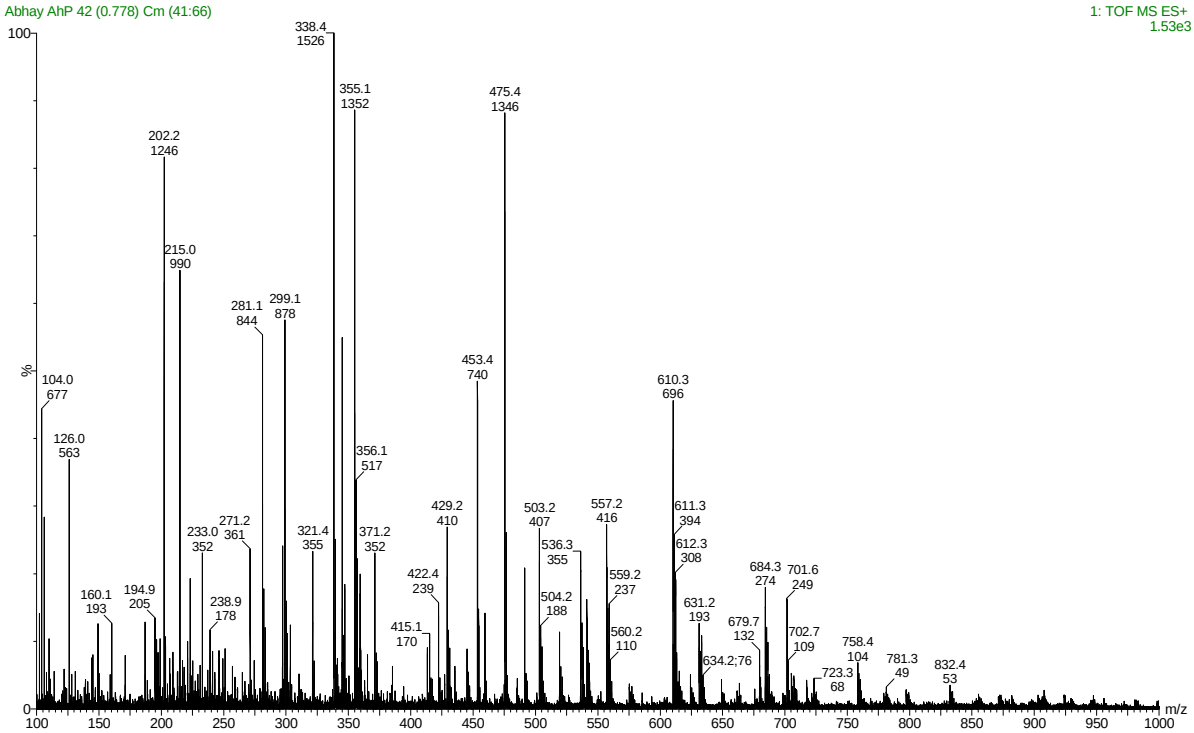

Fig. No.2 Mass spectra of the bio-material

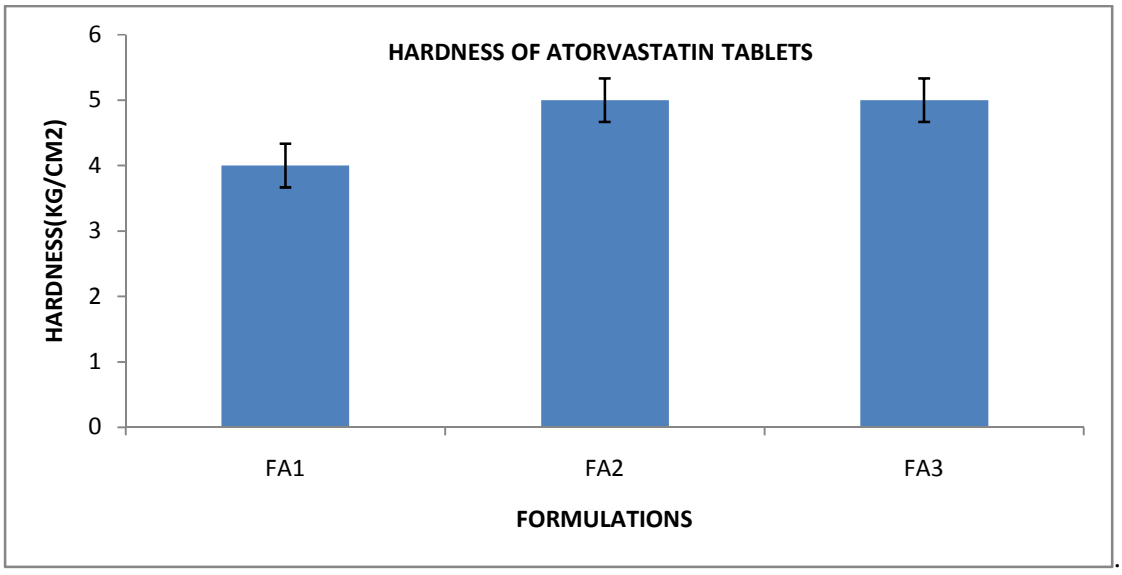

Fig. No.3 Hardness of the tablets

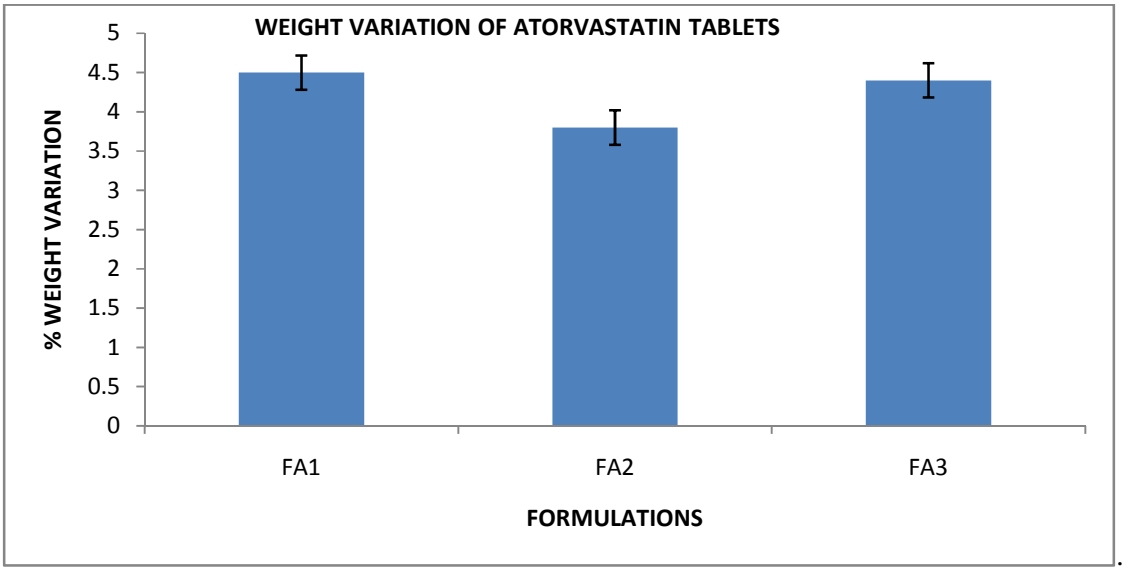

Fig. No. 4 Weight variation of the tablets

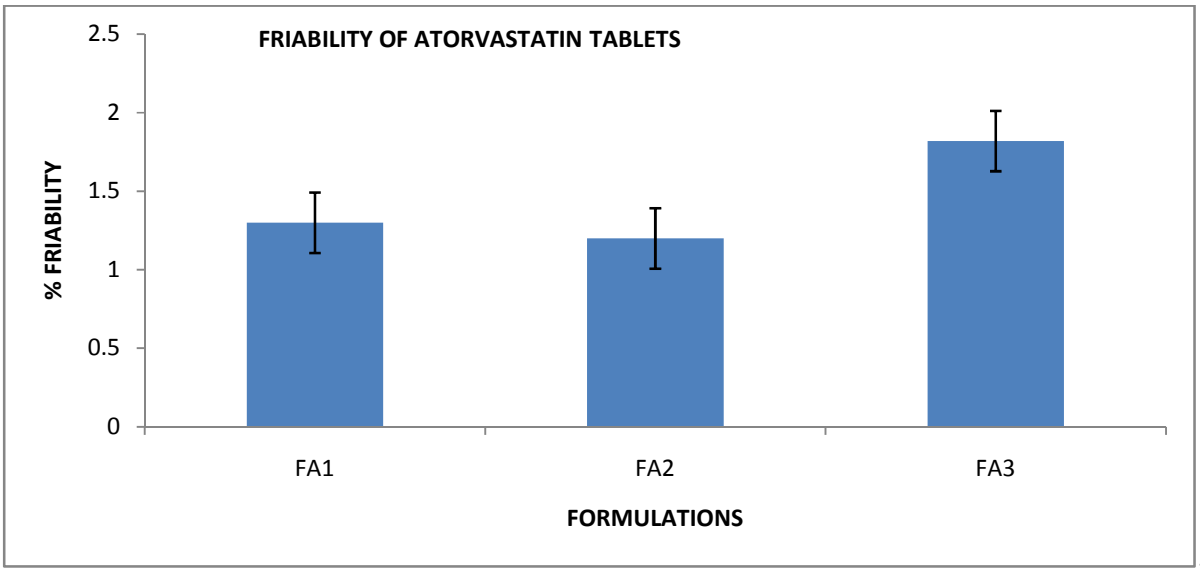

Fig. No. 5 Friability of the tablets

Table no. 3 Drug release kinetics of atorvastatin sustained release tablets

FORMULATION	r^2 (korsmeyer model)	r^2 (higuchi model)
FA1	0.9785	0.9672
FA2	0.9654	0.9972
FA3	0.9935	0.9889

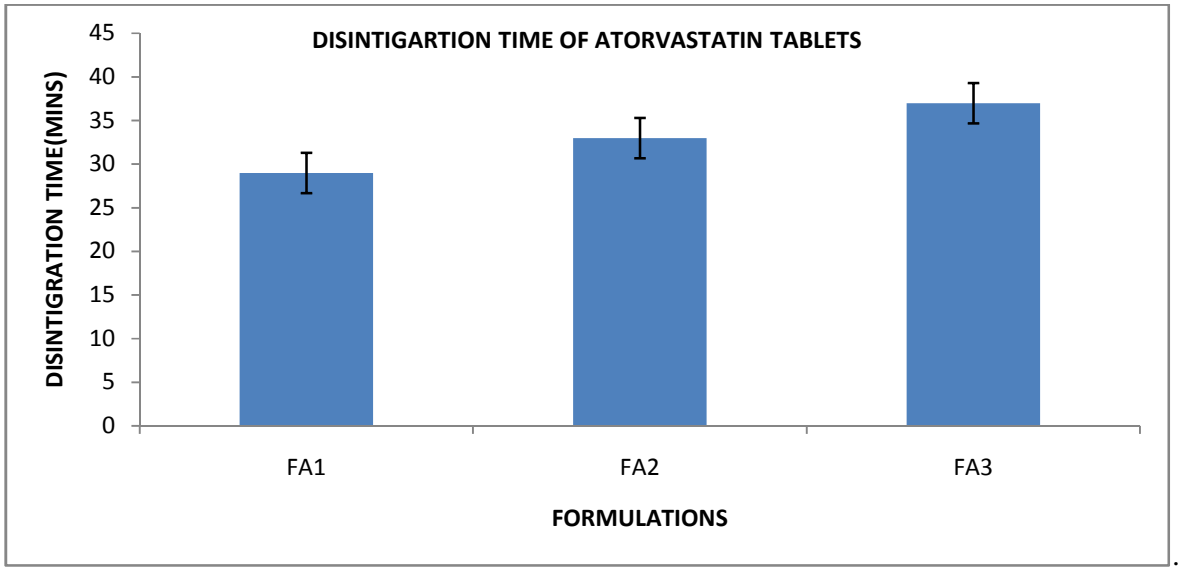

Fig. No. 6 Disintigration time of the tablets

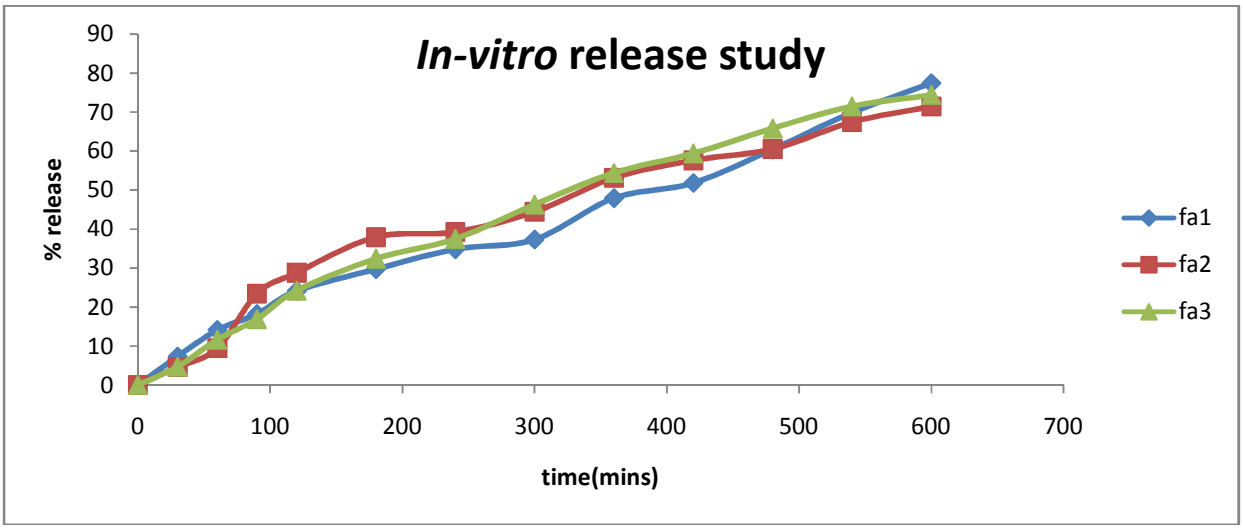

Fig. No.7 *In-vitro* release study of atorvastatin tablets

DISCUSSION

A novel bio-polymer from *Artocarpus heterophyllus* was isolated by simplified economical process the yield was 1% per 100gms. The bio-polymer obtained was of brownish to dark brown colour with a colour changing point of 160-165˚. The bio-polymer showed positive tests for the presence of proteins and carbohydrates. The biomaterial was devoid of signs of toxicity in animals tested. This may be due to the edible nature of the *Artocarpus heterophyllus*.Three different formulations were formulated using various proportions of bio-material for the preparation sustained release tablets of atorvastatin. The release rate kinetic data for all the models is shown in Table 6. Drug release data of tablets was fitted into the Higuchi equation (r^2 = 0.9785, 0.9654 and 0.9935 for batches FA1, FA2, FA3, respectively). Korsmeyer equation (r^2 = 0.9672, 0.9972, and 0.9889, respectively) and indicated combined effect of diffusion and erosion mechanisms for controlled drug release.. The formulations showed a weight variation in the range 3.8%-4.5%, friability of 1.3%-1.8%, hardness of 4-5 kg/cm^2. The formulation FA3 was found to be the best formulation on the basis of t50% and t80%. It showed a t50% of 400mins, and t80% of more than 10 hours.

CONCLUSION

A smart conclusion was drawn that the bio-material can serve as a potential agent for formulating various sustained release formulations for the treatment of various chronic ailments along with the advantages of being non-toxic, biodegradable and free from any adverse effects.

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