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Formulation and Evaluation of Zidovudine Bio-Micro Dwarfs using a Novel Bio-Muco Resident from *Artocarpus heterophyllus*

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Abstract: The current aim of our research work is to isolate a novel bio-material from fruit pulp of *Artocaropus heterophyllus* and to evaluate its muco-retardability by formulating bio-muco dwarfs using zidovudine as model drug. The bio-material was isolated from fruit pulp of *Artocarpus heterophyllus* by simplified economic process. Six zidovudine loaded bio-micro dwarfs were prepared using various ratios of bio-retardant isolated. Our experimental research showed that the isolated bio-material possesses good mucoadhesivity the bio-material also exhibits its synergetic mucoadhesive when combined with sodium carboxy methyl cellulose. Finally the experimental results showed promising observations in terms of particle size, mucoadhesivity and content uniformity. Hence conclusion was drawn that the isolated bio-polymers has shown its potentiality as bio muco resident for formulating mucoadhesive microparticles. The bio-polymer can serve as potential polymer for formulating various drug loaded microparticles.
Key words: Zidovudine Bio-Micro Dwarfs ,Novel Bio-Muco Resident , *Artocarpus heterophyllus.*

INTRODUCTION AND EXPERIMENTAL:

The current aim of our research work is to isolate a novel bio-material from unripe fruit pulp of *Artocaropus heterophyllus* and to formulate bio-muco dwarfs using zidovudine as model drug. The bio-material was isolated from the unripe fruit pulp of *Artocarpuis heterophyllus* by simplified economic process.

Jackfruit (*Artocaropus Heterophyllus)*, belongs to the family moraceae, contains morin, carotenoids, provitamin A. It is used medicinally as a laxative, tonic and demulcent. Zidovudine is a nucleoside analog reverse transcriptase inhibitor (NRTI), a type of antiretroviral drug. Like other reverse transcriptase inhibitors, AZT works by inhibiting the action of reverse transcriptase, the enzyme that HIV uses to make a DNA copy of its RNA. Zidovudine-triphosphate is a competitive inhibitor of, and a substrate for, reverse transcriptase with respect to the thymidine triphosphate (ttp) nucleotide. It was the first approved treatment for HIV.

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. In terms of drug delivery systems bioadhesion or mucoadhesion refers to the attachement of the drug along with a suitable carrier to the mucous membrane.In other terms, mucoadhesion is the attachement of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism,(1)

- Intimate contact between a bioadhesive and a membrane(wetting or swelling phenomenon) (2,3).
- Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane(interpenetration) (2,3).

Mucoadhesion mechanism can be undersood by Wettability theory, Electronic theory, Fracture theory, Adsorption theory, Diffusion theory(1). Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption.(4)

- A mucoadhesion promotoing agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva.
- The various physical and chemical exchanges can effect the polymer/ mucus adhesion, so as polymer should be carefully selected with the following properties in mind.(5)

The bio-material was isolated from fruit pulp of *Artocarpus heterophyllus* by simplified economic process. It was subjected for various physicochemical properties like color, melting point, IR spectral study. Six zidovudine loaded bio-micro dwarfs were prepared using various ratios of bio-retardant isolated. The formulated bio-micro dwarfs were subjected for various evaluation parameters like particle size, content uniformity, Ex- vivo mucoadhesivity, *in-vitro* release studies. Our experimental research showed that the isolated bio-material possesses good mucoadhesivity the bio-material also exhibits its synergetic mucoadhesive when combined with NaCMC. Finally the experimental results showed promising observations in terms of particle size, mucoadhesivity and content uniformity.

MATERIALS:

The model drug zidovudine was obtained from Macloids laboratories ltd., Mumbai as a gift sample. All the reagents were of analytical grade. Double distilled water was used throughout the experiment.

POLYMER EXTRACTION METHOD FROM *Artocarpus heterophyllus:*

The fruits of *Artocarpus heterophyllus* were taken and the outer cover was removed, the fruits were cut, sliced and the fibres removed. 500gms pulp of the fruit was properly crushed in a pestle-mortar, and then subjected to grinding in a mechanical mixer by adding sufficient water to it for 1 hour. The resulting mixture was filtered and the filtrate was centrifuged to remove the residual matter. The supernatant were pooled and to it was added 500ml of 90% ethanol. This solution was kept in a refrigerator for 12 hours, the bio-material was collected by centrifugation at 4000 RPM for 10 mins and dried, triturated sieved by passing through mesh size 120.

PREPRATION OF BIO-MUCORESIDENT BIO-MICRO DWARFS OF ZIDOVUDINE:

Six zidovudine loaded microparticle formulations were prepared by dissolving the drug in 90% ethanol which was added drop by drop to the bio-material solution containing water and sodium carboxy methyl cellulose. Lactose was added as an anti adherent to the bio-material. The drug solution was added to the bio-material solution, followed by the adding dropwise water to cause dehydration resulting in the formation of a turbid solution from which the microparticles were collected.

Among the Six formulations prepared three formulations (AH-1,AH-2,AH-3) were prepared without the use of NaCMC and the other three (AHM-1,AHM-2,AHM-3) were prepared by adding sodium carboxy methyl cellulose. (Table no. 1)

Table no. 1 Formulations prepared

S.NO.	FORMULATION	AH-1	AH-2	AH-3	AHM-1	AHM-2	AHM-3
1.	Biomaterial(mg)	100	50	150	100	50	150
2.	Zidovudine(mg)	100	100	100	100	100	100
3.	Lactose(mg)	100	100	100	100	100	100
4.	NaCMC(mg)	--	--	--	100	50	150

EVALUATION PARAMETERS:

The prepared formulations were evaluated for the following evaluation parameters;

Particle size- The particle size and shape was determined by optical microscopy method.

Content uniformity test- The test was performed by keeping 100mg of microparticles in ethanol and kept for shaking in content uniformity apparatus for 1 hour. After this the solution was filtered and the filterate was analysed by ultra-violet spectroscopy.

Mucoadhesion studies- The mucoadhesion test was performed by using the flow channel or the M.S. apparatus use of goat intestine.

Novel Madhav-Shankar Mucoretentive Study Apparatus. The novel self designed M-S mucoretentive study apparatus by Madhav & Shankar 2009, is a novel apparatus provides a unique platform for mounting the tissue for the mucoretentive study of the dosage device and it produced reproducible data. The apparatus assembled as shown in the figure no.4. The study was conducted by placing a bioplate 2mm diameter, 3 cm away from the narrow open end with the help of a loop. The ringer solution was allowed to pass at a rate of 5ml/min. The solution was continuously allowed to flow until dislodgement of bioplate. The time of dislodgement of bioplate was registered and the entire process was replicated for 6 times using fresh soft palatal tissue and bioplate.. The results were compared with the standard polymers like NaCMC and HPMC.(6,7)

In-*vitro* drug release studies- The dissolution studies were performed by filling the microparticles in an empty capsule and subjecting it for dissolution in USP TYPE II apparatus. The dissolution medium used was phosphate buffer pH 7.4. 5 ml of sample was withdrawn at 30 mins interval and sink conditionn was maintained by replacing with fresh dissolution medium. The dissolution was performed for 8 hours and the samples were analysed by uv spectroscopy method with absorption maximum at 267nm.

RESULTS AND DISCUSSIONS:

PHYSICOCHEMICAL PROPERTIES OF THE BIO-MATERIAL:

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 color with a colour changing point of 160-165˚. The bio-polymer showed positive tests for the presence of proteins and carbohydrates. (Table no.2, Table no.3)

Infra red spectra of the bio-polymer: The IR soectra of the bio-material was performed at MIT, Meerut, U.P., India. The interpretation of the IR spectra is given in table no. 4.

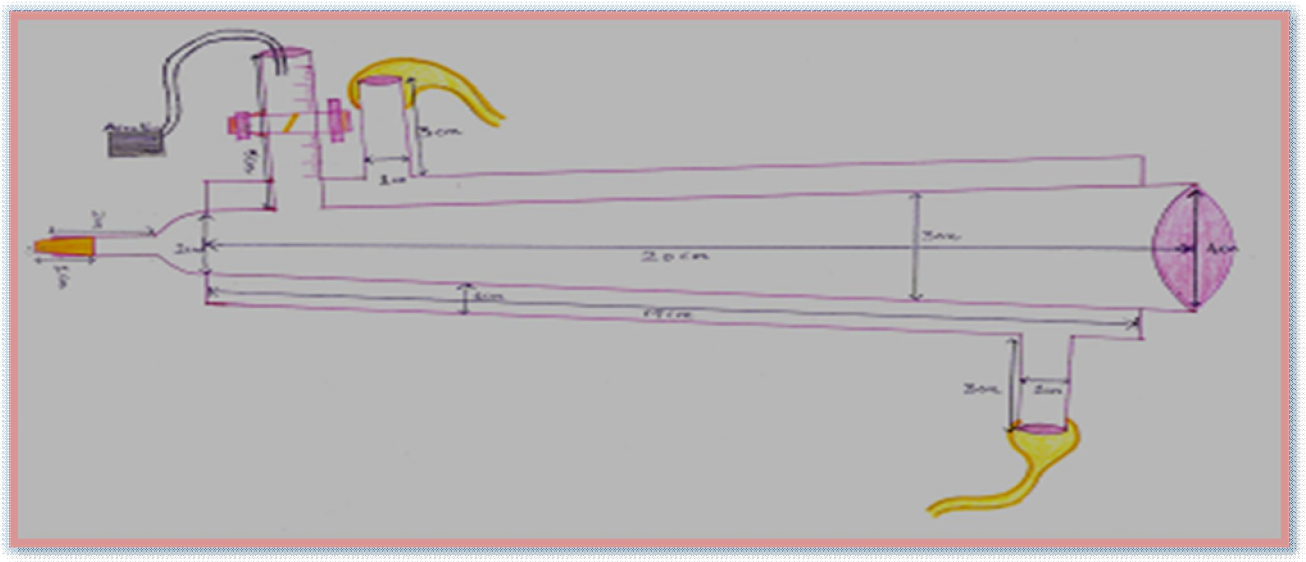

Fig. no. 1 . Novel Madhav-Shankar Mucoretentive Study Apparatus.(6,7)

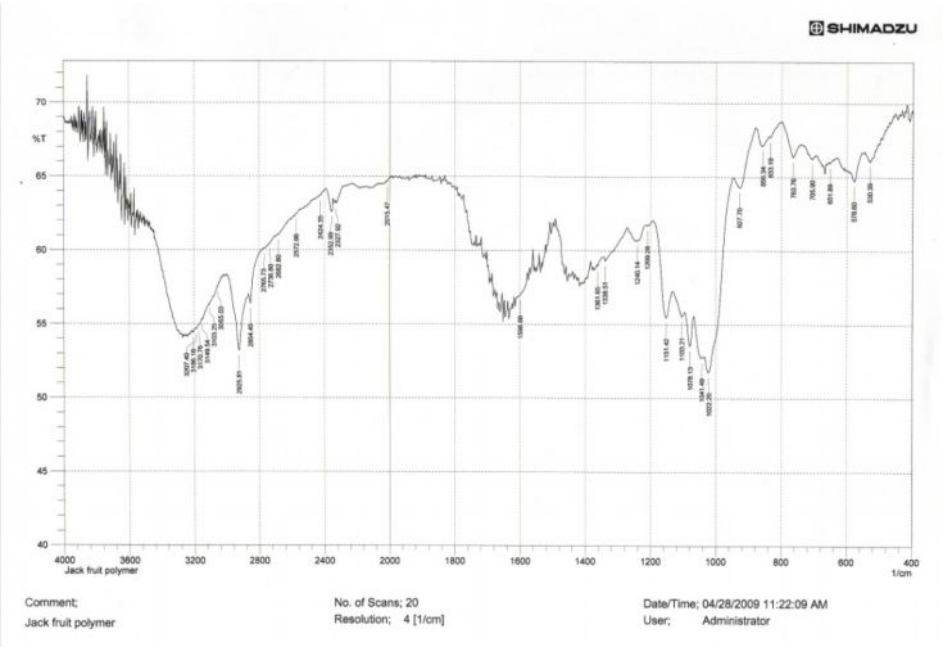

Fig. No. 2 Infra red spectra of the bio-material

Table No.2 Physical Properties of Bio-Material

S.no.	PHYSICAL PROPERTY	INFERENCE
1.	Colour	Brownish To Dark Brown
2.	Odour	Odourless
3.	Taste	Characteristic
4.	Colour changing point	160-165°C

Table no.3 chemical identification tests of the bio-polymer.

S.no.	Chemical test	Observations	Inference
1.	Fehlings test	Positive	Carbohydrates present
2.	Benedicts test	Positive	Carbohydrates present
3.	Molischs test	Positive	Carbohydrates present
4.	Ninhydrins test	Positive	Protiens present
5.	Biurets test	Positive	Protiens present

Table no. 4 Interpretation of the IR spectra

S.No.	Wave number	Inference
1.	2925.81	C-H stretching (Saturated hydrocarbons)
3.	1598.88	C-C stretching (Aromatic ring)
4.	1000-1150	O-H streching (Alcohols)
5.	1078.13	O-H streching (Secondary alcohol)
6.	1151.42	O-H streching (Tertiary alcohol)

EVALUATION PARAMETERS:

Particle size and shape - The microparticles were observed to be irregular, spherical in shape with a particle size in the range 170.3 -183.4µm. formulation AHM-3 showed particle size of 181.4-182.1 and formulation AH-3 showed particle size of 182.1-183.4.(Table no. 5)

Content uniformity test- The content uniformity varied from 73.23% to 85.38% with formulations AH-3 and AHM-3 having the highest content uniformity of 85.38% and 84.34% respectively. (table no.5)

Mucoadhesion studies- The mucoadhesion studies were performed by evaluating the retention time by using novel Madhav Shankar mucoretentive apparatus. The retention time varied from 2 hours 40 mins to 4 hours 20 mins.(fig. no. 4). The formulations AH-3 and AHM-3 showed the highest retention time of 3 hours 30 mins and 4 hours 20 mins respectively. (table no. 5)

***In-vitro* release studies-** The in-vitro release data in all the formulations was performed in zero order, zero-first order, higuchi equation in order to evaluate its release mechanism. The result showed the zero-first order release pattern.(fig. no. 3). Among the six formulations AH-3 had a t50% and t80% of 3.75 and 5.52 hours respectively. Formulation AHM-3 had a t50% and t80% of 2.6 and 5.1 hours respectively. (table no. 5).

Table no. 5 Evaluation parameters

Evaluation Parameter	AH-1	AH-2	AH-3	AHM-1	AHM-2	AHM-3
Particle Size(µm)	170.3-171.4	174.6-174.9	182.1-183.4	177.4-178.3	173.3-173.9	181.4-182.1
Content Uniformity(%)	77.5	82.76	85.38	73.23	78.16	84.34
Mucoadhesivity Test (Retention Time)	3 Hours 10 Mins	2 Hours 40 Mins	3 Hours 30 Mins	3 Hours 50 Mins	3 Hours	4 Hours 20 Mins

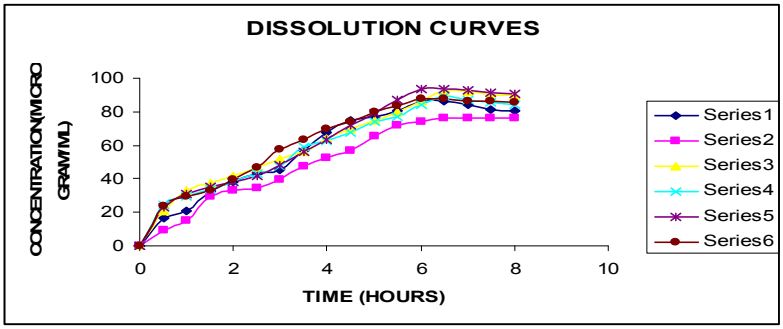

FIG. 3: *In-vitro* release study of the bio-mucodwarfs of zidovudine.

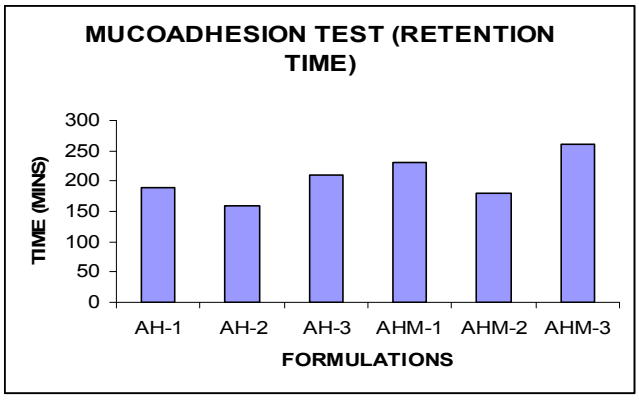

FIG. 4: *Ex-vivo* mucoadhesivity test

DISCUSSIONS:

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. Six different formulations were formulated using various proportions of bio-material for the preparation of bio micro dwarfs of zidovudine. The in-vitro release data in all the formulations was performed in zero order, zero-first order, higuchi equation in order to evaluate its release mechanism. The result shows the zero-first order release pattern.
Among the six formulations; AH-3 shows a content uniformity of 85.4%, particle size range of 182.1-183.4 micrometers. It had a t50% and t80% of 3.75 and 5.52 hours respectively.
Formulation AHM-3 shows a content uniformity of84.3%, particle size range of 181.4-182.1 micrometers. it had a t50% and t80% of 2.6 and 5.1 hours respectively. Hence these two formulations are the best among the six prepared formulations.

CONCLUSION:

Finally the experimental results shown a promising observations in terms of particle size, mucoadhesivity and content uniformity. Hence conclusion was drawn that the isolated bio-polymer has shown its potentiality as bio-muco resident for formulating mucoadhesive microparticles. The bio-polymer can serve as potential polymer for formulating various drug loaded microparticles.

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