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FORMULATION AND EVALUATION OF ZIDOVUDINE SUSTAINED RELEASE MATRIX TABLETS USING MANILKARA ZAPOTA GUM AS A RELEASE RETARDING POLYMER

Dr M.Sunitha Reddy* and Deepthi Dabbeta

Center for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad, Telangana, India.

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***Correspondence for Author**
Dr. M. Sunitha Reddy
Center for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad, Telangana, India.

ABSTRACT

The present study was aimed to develop sustained release matrix tablets of Zidovudine using manilkara zapota gum as a matrix forming hydrophilic polymer. Manilkara zapota gum is a natural drug release rate modifier extracted from the fresh ripens fruits of sapota. Due to the short half life (0.5±3 hrs) Zidovudine sustained release once daily tablet formulation could be used to maintain optimum peak plasma concentration for effective viral suppression. The Zidovudine matrix tablets were prepared by wet granulation method using manilkara zapota gum as a release retarding polymer and polyvinylpirrolidone as a binder. Five formulations of different polymer percentages were formulated, F1 (15%), F2 (25%), F3 (30%), F4 (33%), F5 (25%) is a combination of HPMC: manilkara zapota gum (1:1). The physicochemical characteristics of Zidovudine tablets such as FTIR, melting point, and pre-compression parameters and post-compression parameters were evaluated. All the parameters were found to be within the limits. The dissolution studies were performed using USP apparatus type-II using pH 6.8 phosphate buffer as dissolution medium. These studies showed that formulation F2 consisting of 25% of polymer was found to sustain the release of Zidovudine over a period of 12hrs. The dissolution results show that the increase in gum concentration decreases the drug release.

KEYWORDS: Manilkara zapota gum, Zidovudine, matrix tablet.

INTRODUCTION

Oral administration is the most convenient, widely utilized, most preferred route of drug delivery for systemic action. In long term therapy for treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have many disadvantages. Zidovudine acts as a metabolic antagonist of thymidine analogue and its antiviral effect is time dependent so a sustained release delivery of Zidovudine is desired to maintain antiviral effect and severe side effects. The main limitation to therapeutic effectiveness of Zidovudine is its dose dependent haematological toxicity, low therapeutic index, short biological half life (0.5- 3hr) and poor bioavailability. In the systemic circulation it is first converted to AZT-triphosphate which is pharmacologically active and prevents the replication of virus. The biological half life of AZT-triphosphate is 3 hours and thus requires 3-4 times administration per day. Treatment of AIDS using conventional formulations of AZT is found to have many drawbacks such as adverse side effects due to accumulation of drug in multidose therapy, poor patient convenience, and high cost. Hence sustained release tablets of AZT offers improved bioavailability of drug, decreased dosing frequency and side effects, and improve patient compliance.

The most common method of modulating the drug release is to include the drug in a matrix system. In this study natural polymer is used to prepare matrix tablets because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory profiles. Manilkara zapota gum is used as a matrix forming material which is extracted from fresh ripe fruits of sapota belongs to family Sapotaceae. However the use of hydrophilic matrix alone for sustaining drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymer in the matrix system. In the present work sustained release matrix tablets of Zidovudine using hydrophilic matrix material and in combination with hydrophobic polymer such as polyvinylpirrolidone (PVP) is used.

MATERIALS AND METHODS

MATERIALS

Zidovudine was obtained as a gift sample from Hetero labs, unit-3, Jeedimetla, Hyderabad. The fruits of manilkara zapota Linn were purchased from the local market of Hyderabad. All other materials polyvinylpirrolidone, Microcrystalline cellulose, Talc, Magnesium stearate, HPMC K 100M were of analytical grade and were procured from commercial sources.

METHODS

Isolation of Manilkara zapota gum[1]

The ripe fruit peel and pulp of Manilkara zapota Linn was separated and the seeds were removed. A known weight of (500g) of pulp was soaked in 2000ml of distilled water for 24h, with occasional stirring. The soaked pulp was further ground in grinder and kept for 24h for the release of mucilage with occasional stirring. After 24h, the material was squeezed through an eight-fold muslin cloth to separate the marc from filtrate. Then acetone was added to the filtrate in a ratio (1:3) to precipitate the mucilage. The precipitated mass was separated by decanting and washing 4 times with acetone. The mucilage was subjected to preliminary drying in open air for evaporation of acetone and finally dried in hot air oven at 40^0c, powdered and passed through standard sieve no 80(mesh size160µm). The powdered mucilage was kept in a desiccator until further use.

Characterization of Manilkara zapota gum[1]

Preliminary tests were performed to conform the presence of polysaccharide and to conform the purity. Manilkara zapota gum was characterized for various Organolepic properties such as colour, odour, taste, touch and texture, Physiochemical characterization such as swelling index, pH, solubility, thermal stability, melting point, true density, Micrometric properties such as flow properties(bulk density, tapped density, Angle of repose, Hausner's ratio and Carr's index.) particle size analysis.

The X-ray diffraction studies were conducted for Manilkara zapota gum polysaccharide to determine whether the structure is crystalline or amorphous in nature.

PREPARATION OF MATRIX TABLETS

Five different formulations of Zidovudine were prepared by wet granulation technique using manilkara zapota gum as a matrix forming polymer and polyvinylpirrolidone (PVP) as a binder. Zidovudine, Manilkara zapota gum, polyvinylpirrolidone (PVP), magnesium stearate, microcrystalline cellulose, talc were weighed accurately and shifted through sieve # 100 mesh. Wet granules were prepared by using PVP binder solution and the granules are dried in oven at 50^0c. To the dried granules add magnesium stearate and talc the granules are then subjected for suitable compression using Tablet compression machine.

Table 1: Zidovudine formulation series

Ingredients	F1	F2	F3	F4	F5
Zidovudine(mg)	300	300	300	300	300
Manilkara zapotagum(mg)	125	150	175	200	75
HPMC k100(mg)	-	-	-	-	75
PVP (mg)	q.s	q.s	q.s	q.s	q.s
Microcrystalline cellulose(mg)	155	130	105	80	130
Talc (mg)	12	12	12	12	12
Magnesium stearate(mg)	8	8	8	8	8
Total weight (mg)	600	600	600	600	600

Evaluation of matrix tablets

The formulated tablets were evaluated for the following parameters.

1. Thickness

The thickness of the formulated tablets was measured by using Vernier caliper.

2. Weight variation

The formulated tablets were evaluated for uniformity of weight.20 tablets were weighed together and individually. From the total weight, average weight was calculated. Each tablet weight was then compared with average weight to make certain whether it is within acceptable limits or not.

$$\%\text{Deviation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

3. Hardness

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

4. Friability

The Roche friability tester was used to determine friability of tablets.pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The % friability was calculated using the formula

$$\%\ \text{friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

5. Drug content

Zidovudine 20 tablets are weighed and powdered. An accurately weighed quantity of powder is then dissolved in methanol and analyzed by preparing appropriate dilutions.

6. Invitro drug release studies

The release rate of Zidovudine matrix tablets was determined using USP Dissolution type II testing apparatus (paddle type). The dissolution test was studied in 900ml of phosphate buffer 6.8pH for 12 hours at 37±0.5^{0}c and at 50 rpm. Aliquots of 10ml were withdrawn hourly from the dissolution media for 12hrs and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution amount of drug release was calculated from the calibration curve.

7. Kinetic Model Data Analysis

The dissolution data of controlled release formulation was fitted to kinetic models i.e., zero order release rate kinetics, first order release rate kinetics, Higuchi release kinetics, Hixson-Crowell model and korsmeyer –peppas kinetic model to find out the drug release pattern and mechanism.

8. Stability studies

The best formulation was sealed in aluminium foil and kept in humidity chamber maintained at 40 ±2°c/ 75±5% RH for a period of three months.

RESULTS

CHARECTERIZATON OF GUM

Table 2: Determination of purity of Manilkara zapota gum

Test for Phyto- constituents	Result
Carbohydrates	present
Proteins	absent
Starch	absent
Reducing and non reducing sugars	absent
Alkaloids	absent
Steroids	absent
Tannins and phenol compounds	absent
Glycosides	absent

Table 3: Organolepic properties of gum

Property	Inference
Colour	Brownish
Odour	Agreeable odour
Taste	Tasteless
Texture	Rough
Touch	Hard

Table 4 physicochemical characterization

Swelling index	15ml
pH	6.8
Melting point	180-190^{0}c
Moisture content	9.67%
Loss on drying	5%
Viscosity of 1% solution	14cps

Table 5 Micromeritic properties of gum

Tapped density	**1.83**
Bulk density	0.86
Angle of repose	36.79
Hausner's ratio	1.19
Compressibility index	16.50

The X- RAY diffraction studies of manilkara zapota gum does not show any characteristic peak, which indicates that it is amorphous in nature.

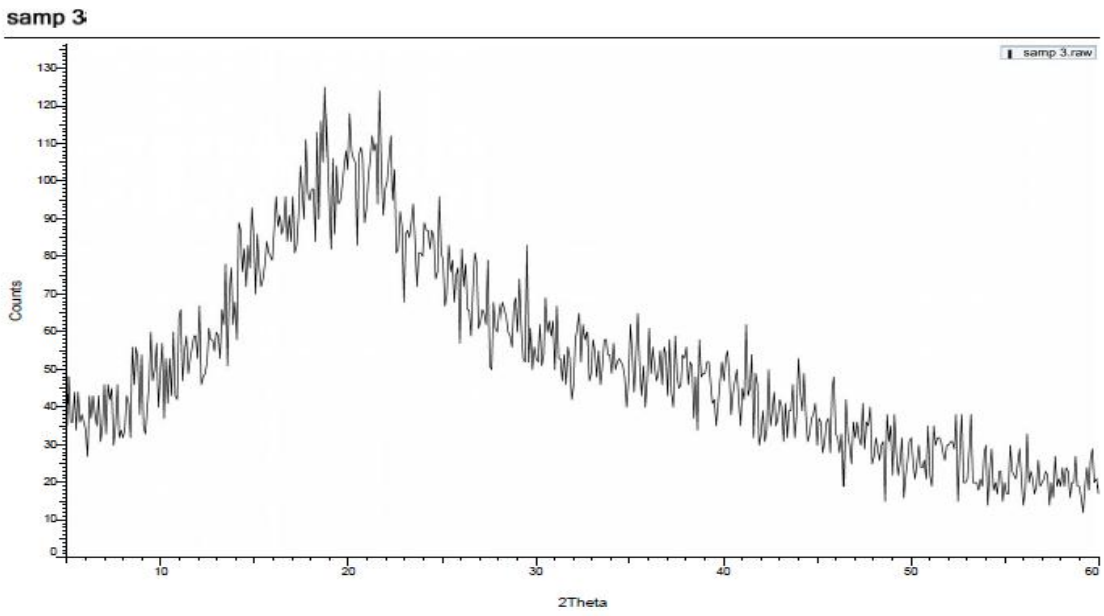

Figure 1: X-Ray spectra of Manilkara zapota gum

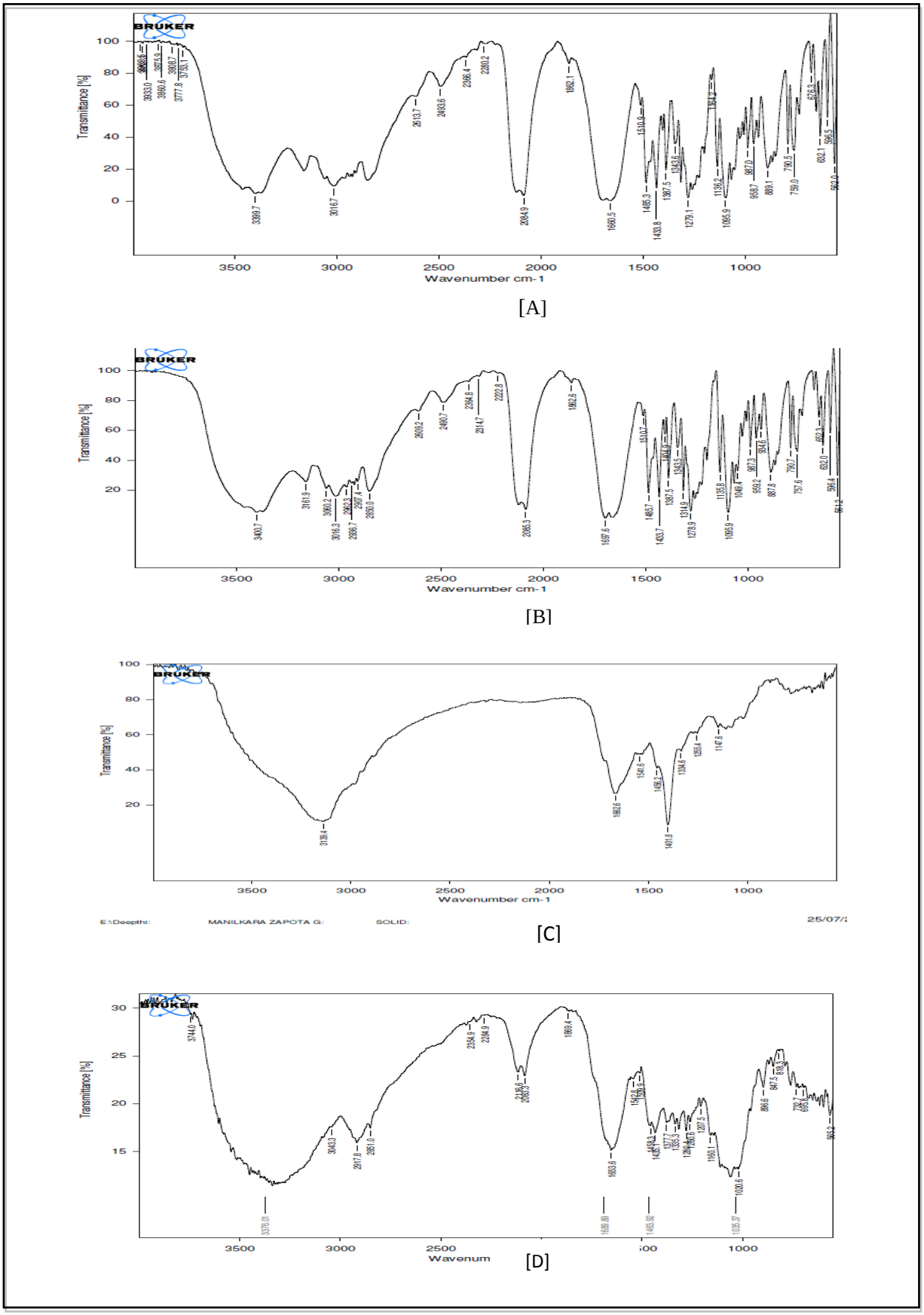

Figure 2: A- FTIR spectra of Zidovudine, B-Zidovudine + manilkara zapota gum, C-manilkara zapota gum and D- optimized formula.

Table 6 Charecterization Of Powders

Formulation (F)	Angle of repose(Ɵ)	Bulk density (gm / cm3)	Tapped density (gm / cm3)	Hausner's ratio	Compressibility index(%)
F-1	29.24±0.5	0.41±0.03	0.46±0.07	1.19±0.06	13.46±0.62
F-2	27.4±0.7	0.39±0.01	0.45±0.04	1.13±0.09	13.34±0.43
F-3	26.29±0.4	0.37±0.02	0.45±0.05	1.15±0.02	13.32±0.34
F-4	27.17±0.3	0.46±0.08	0.49±0.04	1.11±0.04	14.01±0.56
F-5	26.16±0.4	0.34±0.07	0.40±0.03	1.10±0.08	13.02±0.21

Mean ±SD n=6

Table 7: Evaluation Of Tablets

Formulation (F)	Hardness (kg/cm2)	Thickness (mm)	Friability (% w/w)	Content uniformity (%)	Weight variation(mg)
F-1	6.2±0.5	3.5±0.03	0.89±0.12	98.94±0.18	590±1.12
F-2	6.5±0.67	4.6±0.02	0.82±0.09	98.95±0.92	595±1.32
F-3	7.2±0.48	5.4±0.04	0.75±0.05	99.05±0.43	615±2.54
F-4	6.7±0.44	5.8±0.07	0.68±0.14	101.2±0.36	618±3.12
F-5	6.8±0.42	5.2±0.06	0.62±0.07	99.52±0.25	620±2.16

Mean ± SD, n=6

Table 6: Dissolution Data For Different Formulations

Time	F1 (%DR)	F-2(%DR)	F-3(%DR)	F-4(%DR)	F-5(%DR)
0	0	0	0	0	0
1 hour	17.599±1.40	16.58±2.61	15.62±1.65	11.18±1.21	12.13±2.09
2 hour	35.599±2.08	22.14±3.16	20.12±2.17	16.23±2.23	19.03±2.34
3 hour	55.15±1.65	31.66±2.02	25.09±1.09	19.11±3.15	26.72±1.62
4 hour	78.52±3.02	39.57±1.62	36.86±3.05	27.03±2.10	34.04±1.58
5 hour	83.36±3.12	47.66±1.63	41.51±1.76	33.38±1.29	43.6±3.02
6 hour	97±1.67	51.03±2.17	50.35±2.07	37.8±3.18	50.45±2.19
7 hour		61±1.89	54.06±3.01	47.48±1.21	58.12±3.13
8 hour		64±2.19	64.58±1.09	53.26±2.09	65.07±2.47
9 hour		72.07±2.18	72.16±2.02	57.07±3.12	70.13±0.67
10 hour		83.17±3.04	80.13±1.68	69.13±2.19	79.33±2.03
11 hour		89.16±1.34	90.19±0.92	83.18±0.97	85.12±3.13
12 hour		99.26±0.15	94.29±1.03	90.12±1.12	87±2.25

Mean ±SD, n= 6

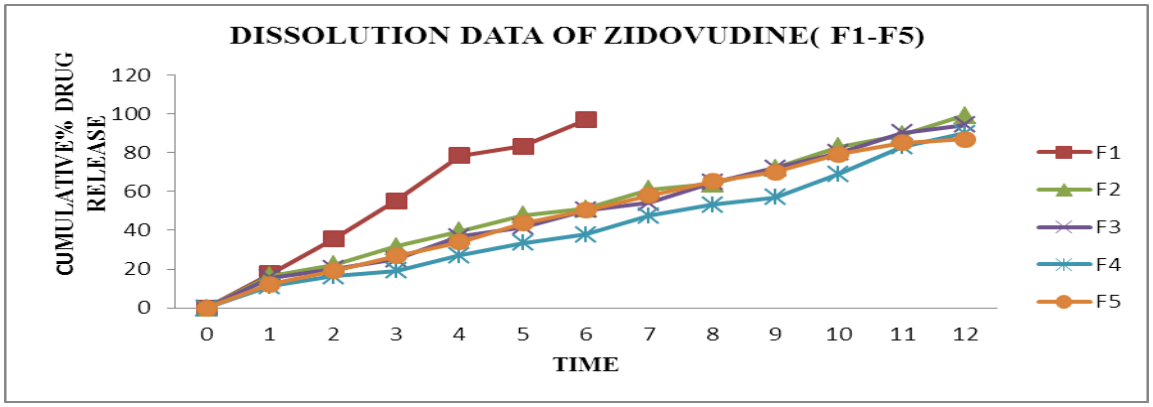

Figure 3: Invitro Dissolution profiles of formulations F1, F2, F3, F4, F5

Table 8: kinetic values of Zidovudine formulations

Kinetic model	R^2 Value
Zero order	0.990
First order	0.666
Higuchi model	0.967
Korsmeyer peppas	0.896

Table 9: Accelerated stability studies of optimized formula

S. No	Parameters	Initial	After one month	After three month
1	colour	Cream	Cream	Cream
2	Odour	No	No	No
3	Texture	smooth	smooth	Smooth
4	Thickness(mm)	3.4±0.6	3.5±0.3	3.3±0.7
5	Hardness(kg/cm^2)	6.2±1.2	6.2±1.0	6.2±1.1
6	Friability(%W/V)	0.52±0.012	0.53±0.01	0.54±0.02
7	Weight variation(mg)	599±2.342	597±4.158	602±2.147
8	Assay	99.06±0.12	99.08±0.17	99.12±1.3
9	Percentage drug release (%)	99.17±0.12	99.12±0.09	99.09±0.10

DISCUSSION

In this study sustained release tablets of Zidovudine were prepared using pharmaceutically acceptable and easily available excipients by wet granulation method. Zidovudine was tested for its identification by UV spectrophotometer and FTIR spectrum. From the UV study it was observed that the absorption maxima Zidovudine in 0.1N HCl and 6.8pH phosphate buffer was found to be 266nm and 267nm respectively.

FTIR spectra of Zidovudine, manilkara zapota gum and their physical mixture, optimized formula were taken. All the characteristic peaks of pure drug i.e.; C-N Amine Stretching (1030-1250cm-1), N-H Stretching (3200-3500cm-1), C=O Stretching (1600-1700cm-1), O-H Stretching (3100-3400cm-1), were observed in the spectrums of Drug Zidovudine and

Manilkara zapota gum mixture, optimized formula too. This indicates that there is no polymer interaction between drug and polymer. Precompression parameters like Angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner's ratio are tested and found to be within acceptable limits(Table:2) Manilkara zapota gum used in different concentrations like 15%, 25%, 30%, 33% . An increase in concentration of manilkara zapota gum significantly prolongs the drug release. Here the main mechanism in controlling the drug release is Diffusion but not the dissolution. The Resulted Matrix tablets are evaluated for the parameters like Hardness, weight variation, friability, and content uniformity and results are fond to be satisfactory. Manilkara zapota gum is a hydrophilic matrix forming agent it is useful to control the drug release of both water soluble as well as water insoluble drugs from formulations. Sustained release Zidovudine dosage form could reduce the dosing frequency and improve patient compliance. Faster release of the drug from the hydrophilic matrix was probably due to faster dissolution of the highly water soluble drug from the core and its diffusion out of the matrix is a rate controlling step. The manilkara zapota gum sustains the drug release up to 12hrs.manilkar zapota gum sustain the release by increasing the distance required for drug to travel from tablet to dissolution medium. Furthermore, Formulations F1-F5 containing Manilkara zapota gum in different concentration shows the extended drug release for up to12 hrs, among all the formulations, F2 is considered as optimized formulation because it shows drug release pattern acc to USP. Drug release of optimized formulation also compared with the marketed immediate release dosage form. To investigate the drug-release kinetics, obtained data fit to various kinetic models (Table: 8) such as zero-order, first-order, Higuchi equation and Korsmeyer–Peppas equation. The zero order shows higher R2 values for batch F2 ($r2$ =0.990).

CONCLUSION

Results of the present study demonstrated that the sustained-release matrix tablets of AZT can be prepared by employing manilkara zapota gum alone. The investigated sustained release matrix tablet was capable of maintaining constant plasma AZT concentration through 12 hours. A total number of five different formulations were prepared with increasing concentration of the polymer. It can be concluded form the research study that among the prepared formulations, F2 (99.26%) is the best formulation. This can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional AZT tablets. In the present investigation, Zidovudine

matrix tablets were successfully fabricated using selected polymer and evaluated for its sustained release properties.

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