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COMPARITIVE STUDIES OF HYDROPHILIC POLYMERS ON SUSTAINED DRUG DELIVERY OF ZIDOVUDINE

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Keywords:

Sustained drug delivery, karaya gum, kondagogu gum, synthetic polymer HPMC(K100)

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ABSTRACT

The goal in designing sustained or controlled delivery is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[6] Considering the scope and availability of the natural polymers the present research work was planned with karaya gum, kondagogu gum and synthetic polymer HPMC(K100) as matrixing agents for the sustaining the drug release.

INTRODUCTION

Oral route is the most popular route used for administration of drugs, due to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. Tablets are one of the most stable and commonly administered oral dosage forms. Tablets remain popular as dosage form because of the advantages afford both to the pharmaceutical manufacturers and patients. Because of simplicity and economy of preparation, stable and convenient in packing, ease of transporting and dispensing, accuracy of single dosage regimen. [1] Conventional oral drug administration does not usually provide rate controlled release or target specificity. In many cases conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level. [2] The drug concentration eventually drops off until readministration. In order to obtain maximum therapeutic efficacy, it becomes necessary to deliver active agent to the target tissue in the optimal amount for the required period, thereby causing little toxicity and minimal side effects. [3] Zidovudine is a nucleoside reverse transcriptase inhibitor a type of retroviral drug used for the treatment of HIV/AIDS infection. it works by selectively inhibiting the reverse transcriptase enzyme responsible for the virus to make a DNA copy of its RNA.[4,5]. Zidovudine has low therapeutic index, short biological half-life, and poor bioavailability, due to short biological half life the patient need frequent administration of drug. It leads to an adverse side effect by inhibiting the DNA polymerase is used by human cells to undergo cell division due to an accumulation of drug The reason behind in formulating sustained release dosage forms is to reduce the frequency of dosing, reducing the dose required, and better patient compliance. Due to the sustaining nature of drugs therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time. Tablets are the most widely used formulations available in the market preferred by patients and physicians. In the treatment of chronic diseases conventional tablets are to be administered in multiple doses, due to this drawback in conventional formulations there is a need to develop sustained release formulations for such chronic diseases.[6,7].

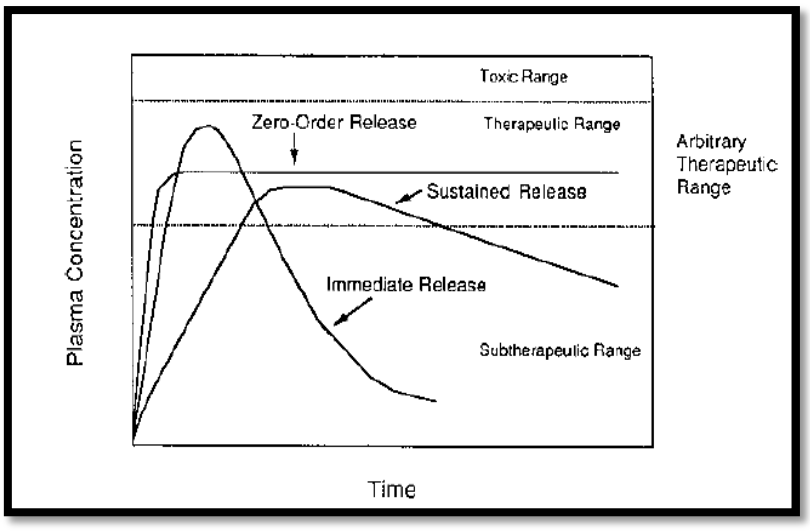


Fig 1: Drug level versus time profile showing differences between zero order control release, slow first order sustained release and release from a conventional tablet or capsule

MATERIALS AND METHOD

All the materials used for the research work were of analytical grade. Materials used in the formulation of matrix tablets were listed in the following table.

LIST OF MATERIALS USED:

Zidovudine, hupu gum, Sterculia gum, HPMC(K100), Lactose, Magnesium Stearate, Talc, Sodium hydroxide, Potassium dihydrogen ortho phosphate, Hydrochloric acid, Ethanol.

PREPARATION OF BUFFER SOLUTIONS.

Preparation of 0.1 N HCl: Accurately measured 8.5 mL of concentrated hydrochloric acid was added to 1000 mL of distilled water.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water.

Preparation of pH 6.8 phosphate buffer: 250 ml of 0.2 m potassium di hydrogen phosphate was placed in 1000ml volumetric flask. 112 ml of 0.2M NaoH was added and then the volume was adjusted with distilled water up to 1000ml. pH was adjusted to 6.8 with diluted sodium hydroxide.

CONSTRUCTION OF CALIBRATION CURVE FOR ZIDOVUDINE

Preparation of Standard solution: 100 mg of zidovudine was accurately weighted into 100 m1 volumetric flask and dissolved in small quantity of methanol; the volume was made up

with the ethanol. Pipette 10 ml of above solution into another 100 ml of volumetric flask and the volume was made with the 0.1 N HCL.

Preparation of working standard solution: Aliquots of standard solution from 0.5ml, 1ml, 1.5ml, 2ml, and 2.5ml, were pipette into 10ml volumetric flasks. The volume was made up with 0.1 N Hcl. The absorbance was measured at 270 nm using 0.1 N HCL as a blank.

Similarly, standard graph was plotted with pH 6.8 phosphate buffer. The results of calibration curve were given in Table No 8 (a) (b) .

Method: UV spectroscopy

Equipment: SL-Elico- 159 single beam UV- visible spectrophotometer.

Buffers used: P^H 1.2, 6.8 phosphate buffer

PREPARATION OF MATRIX TABLETS

All the matrix tablets, each containing zidovudine 300 mg, were prepared by direct compression method. Formulations were prepared using different concentrations of Hupugum, sterculiagum and HPMC (K100M) as retarding materials and lactose as diluents. The formulations were given in Table No 5. Above polymers are used as matrixing agents. The formulations were listed in the Table No 6. Drug and diluents were mixed with different concentrations of polymers for 20 minutes. These blended with lubricating agents (1% w/w magnesium stearate and 1% w/w talc) and compressed using 16 station rotary punching machine, equipped with flat-faced, round punches of 12-mm diameter.

Drug polymer compatibility:

Drug polymers interactions were studied by FT-IR spectroscopy. About 50mg of zidovudine pure drug, physical mixtures of drug and polymers (1:1) were weighed and mixed uniformly. The IR spectrum of the powder from 400-4000cm^{-1} was recorded.

Table 1: Composition of matrix tablets formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zidovudine(mg)	300	300	300	300	300	300	300	300	300
SG(mg)	15	30	45	-	-	-	-	-	-
HG(mg)				15	30	45	-	-	-
HPMCk100(mg)	-	-	-	-	-	-	15	30	45
Lactose(mg)	165	150	135	165	150	135	165	150	135
Mg state(mg)	10	10	10	10	10	10	10	10	10
Talc (mg)	10	10	10	10	10	10	10	10	10
Total weight(mg)	500	500	500	500	500	500	500	500	500

Determination of drug content (assay)

1^{O} Stock Solution: The assay for the drug content was carried out by weighing five tablets and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate weighed accurately powder which is equivalent to 100 mg of zidovudine in 100 ml of volumetric flask containing few ml of ethanol and sonic ate for 10min and make up the volume up to 100 ml with methanol.

2^{O} Stock Solution: Pipette out 10 ml from the 1^{O} stock solution into another 100 ml of volumetric flask and make up the volume with 6.8phosphate buffer.

***IN VITRO* DRUG RELEASE CHARACTERISTICS.**

The *in vitro* drug release studies were assessed by USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml of 0.1N Hcl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 10 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 276 nm. Cumulative percent drug released for the formulations prepared using the polymers were given in Table No 13 and 14 and the Figure No's(10 – 13).

KINETIC ANALYSIS OF DISSOLUTION DATA.

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism of drug release from the matrix tablets, the release data was fitted into various mathematical models viz., Zero order, first order, Highuchi equation and peppas equation. In this by comparing the r-values obtained, the best-fit model was selected.

Zero Order Kinetics:

$$Q_t = Q_0 + K_0 t$$

Q_t = Amount of drug dissolved in time t,

Q_0 = Initial amount of drug in the solution and

K_0 = Zero order release constant.

First Order Kinetics:

$$LogQ_t = logQ_0 + \frac{K_1 t}{2.303}$$

Q_t = Amount of drug released in time t,

Q_0 = Initial amount of drug in the solution and

K_1 = First order release constant

Higuchi model:

$$Q_t = K_H t^{1/2}$$

Q = Amount of drug released in time t and

K = Higuchi dissolution constant.

Peppas Release Model:

$$Log\left(\frac{M_t}{M_\alpha}\right) = LogK_{KP} + n\log t$$

Mt / Mα = Fraction of drug release,

K= Release constant,

t = Drug release time and

n = Diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form

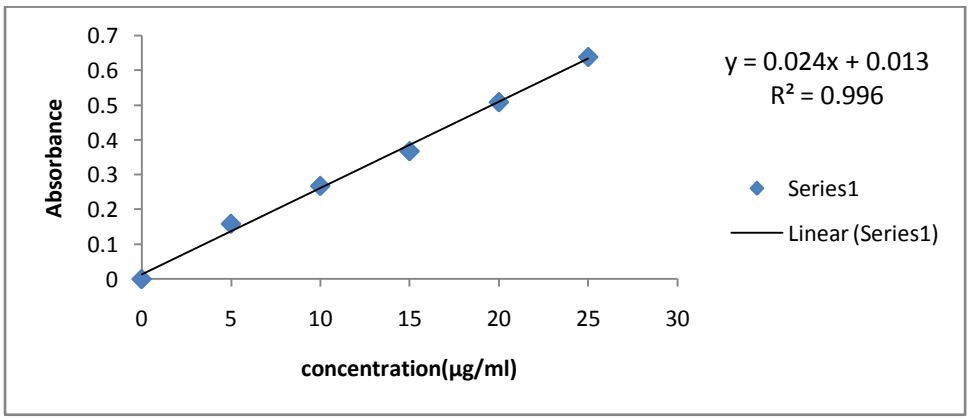
Where, n= number of dissolution sample times and R_t and T_t are the individual percentages dissolved at each time point t for the reference and test dissolution profiles respectively.

RESULTS AND DISCUSSION

Standard graph of zidovudine

The standard graph of zidovudine has shown good linearity in concentration of 5 to 25 mcg/ml with regression coefficient of 0.994 in pH 1.2 and 0.996 in phosphate buffer pH 6.8 (Table No 6.1 and Figure No 6.1), phosphate buffer, respectively.

Figure: Calibration curve of the zidovudine in p^H 1.2and p^H 6.8phosphate buffer at 270nm.



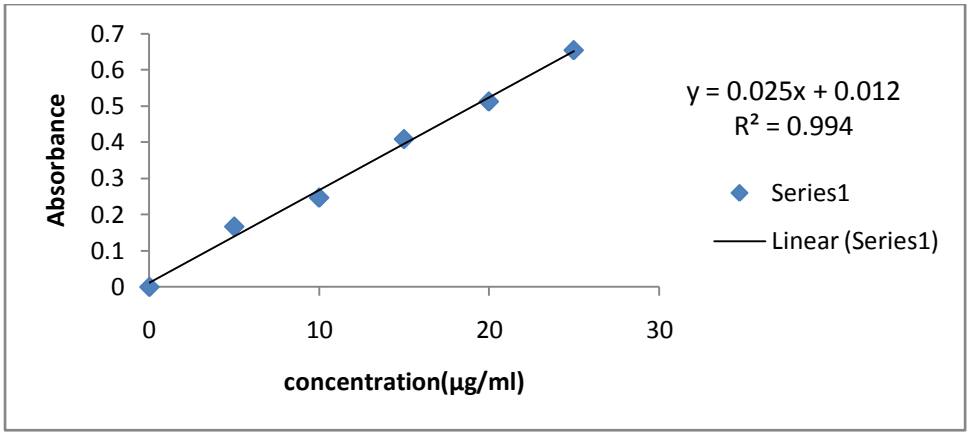


Figure 2: Calibration curve for zidovudine in P^H1.2 buffer at 270nm

Table 3: Optical characteristics and stastical data of regression equations

S.NO	Parameter	P^H 1.2	P^H 6.8 buffer
1	Absorption maximum	270	270
2	Beers-law limit	5-25mcg/ml	5-25mcg/ml
3	Coefficient of correlation	0.995	0.991
4	slope	0.024	0.026

Dissolution profile of innovator product (zidovir)

Table 4: Innovator Product Dissolution Profile

Time points	Innovator % drug release
0	0%
1	24.1%
2	30.7%
3	35.6%
4	38.9%
5	46.3%
6	50.8%
7	55.7%
8	69.1%
9	78.2%%
10	85.6%
11	92.7%
12	98.9%

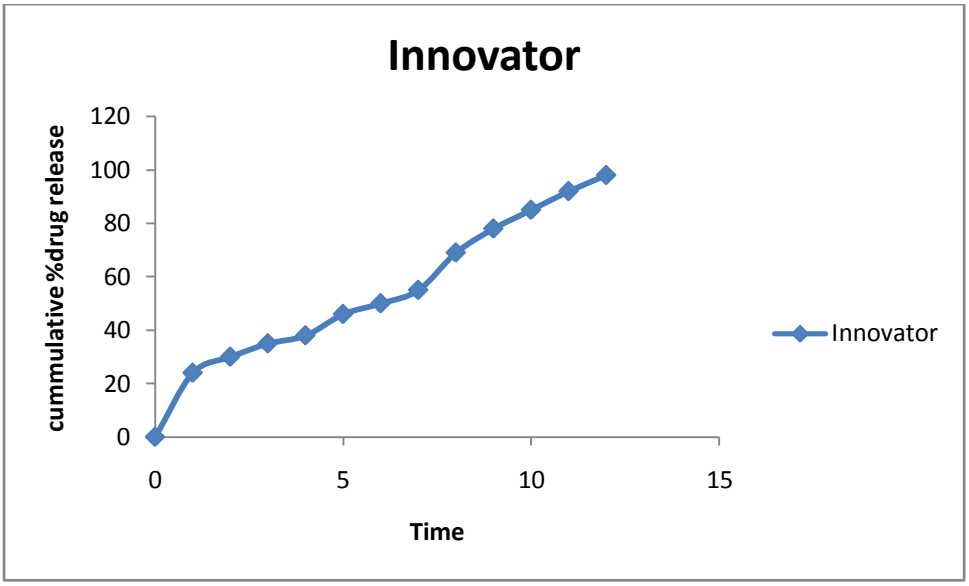


Fig. 3: Cumulative % drug release Vs time profile of innovator product

Conclusion: Zidovudine innovator product (Zidovir) has shown 98.9% drug release in 12 hours. The results were shown in table No 6.3.

Solubility profile

Table 5: Solubility data of zidovudine

Solvent media	Solubility (mg/ml)
Water	28.10
0.1 HCl	27.51
pH 4.5 buffer	21.36
pH 6.8 buffer	20.10

Conclusion: The above values of concentrations indicate the solubility of zidovudine in different solvents. It was observed that the solubility of zidovudine in acidic media is very high and it shows normal solubility profile in pH 6.8 buffer. The results were shown in table No 6.4.

Table 6: Physical, Micromeritic and Rheological characterization of the polymer and drug

PARAMETERS	KARAYA GUM	KONDAGOGU GUM	HPMC(K100M)	ZIDOVUDINE
Viscosity (cps)	1183.23	1313.66±3.278	8407.65	-
p^H	4.19	4.20±0.008	6.86	
Ash content (%)	8.15	7.51±0.016	-	-
Melting point (°c)	-	-	--	283-285°c
Angle of repose(°)	31.18±2.122	33.20±0.0122º	35.25±0.98	36.56±0.609º
Bulk density(g/ml)	0.55±0.08	0.645±0.000	0.4±0.005	0.468±0.006
Tapped density(g/ml)	0.621±0.005	0.740±0.002	1.11±0.006	0.576±0.008
True density(g/ml)	1.17±0007	1.366±0.001	1.268±0.004	1.24±0.154
Carr's index (%)	11.53±0.571	12.83±0.223	63.96±0.001	18.75±2.023
Hausner ratio	1.13±0.006	1.147±0.002	2.7±0.002	1.230±0.031

Table 7: Pre compression parameters of formulation blends

Formulation	Angle of repose(˚)	Bulk density(g/ml)	Tapped density(g/ml)	Cars Index(%)	Hausner ratio
F1	29.59±1.973	0.570±0.004	0.605±0.011	5.83±1.215	1.05±0.015
F2	27.4±1.25	0.565±0.001	0.619±0.008	6.01±1.147	1.06±0.001
F3	28.76±0.647	0.595±0.002	0.638±0.004	6.04±0.141	1.048±0.007
F4	29.59±0.121	0.601±0.004	0.646±0.009	5.07±0.08	1.06±0.007
F5	24.61±0.563	0.625±0.004	0.681±0.024	5.45±0.791	1.08±0.005
F6	22.41±0.143	0.654±0.009	0.688±0.005	5.52±0.702	1.05±0.017
F7	27.51±0.645	0.585±0.008	0.627±0.004	4.76±0.745	1.032±0.001
F8	28.2±0.540	0.611±0.007	0.601±0.001	5.30±0.046	1.042±0.015
F9	26.45±0.134	0.599±0.021	0.688±0.003	5.9±0.763	1.05±0.01

Table 8: Physical characteristics and drug content of zidovudine matrix tablets

Formulation	Hardness (Kg/cm^2)	Friability (%)	%Drug content
F1	5.93±0.23	0.43	96.5±1.501
F2	5.6±0.2	0.67	96.2±1.735
F3	5.93±0.23	0.82	99.5.±1.322
F4	6.33±0.11	0.48	98.8±1.616
F5	6.46±0.11	0.25	99.6±2.193
F6	6.4±0.2	0.36	97.8±1.014
F7	6.26±0.11	0.61	97.5±2.151
F8	5.93±0.23	0.54	99.9±1.882
F9	5.86±0.11	0.39	98.6±1.442

Table 9: Swelling index for the formulations using polymers (mean ± S.D; n=3)

FORMULATIONS	2hr	4hr	6hr	8hr	10hr
F1	1.84	2.245	2.547	2.682	2.769
F2	1.96	2.196	2.489	2.699	2.869
F3	2.058	2.258	2.498	2.693	2.964
F4	1.69	1.95	2.305	2.689	2.784
F5	1.84	2.054	2.258	2.524	2.968
F6	1.92	2.109	2.587	2.621	3.15
F7	2.057	2.426	2.694	2.867	2.963
F8	2.258	2.487	2.596	2.674	3.217
F9	2.459	2.567	2.894	3.105	3.547

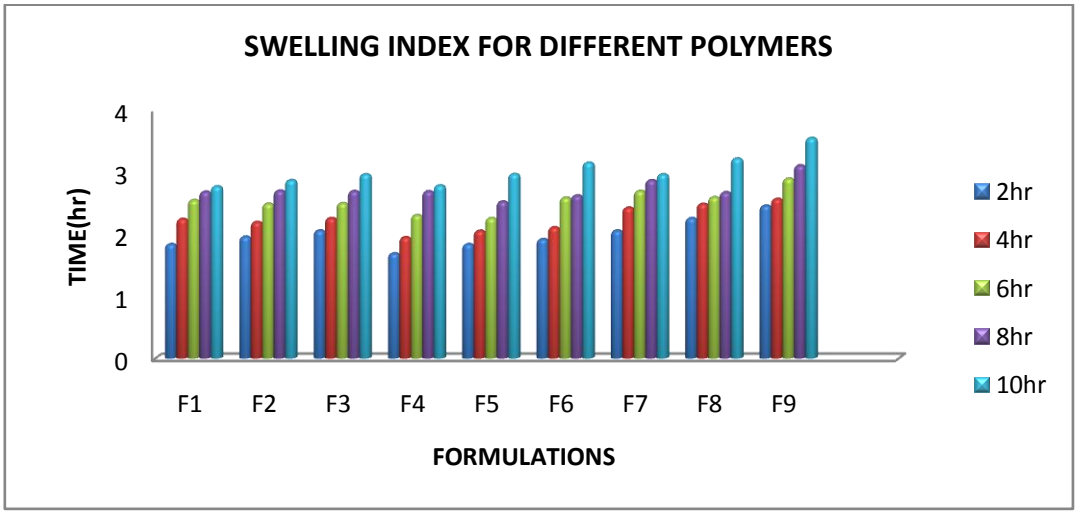


Figure 4: Comparative swelling index for zidovudine formulated using polymers

FT-IR spectra of zidovudine

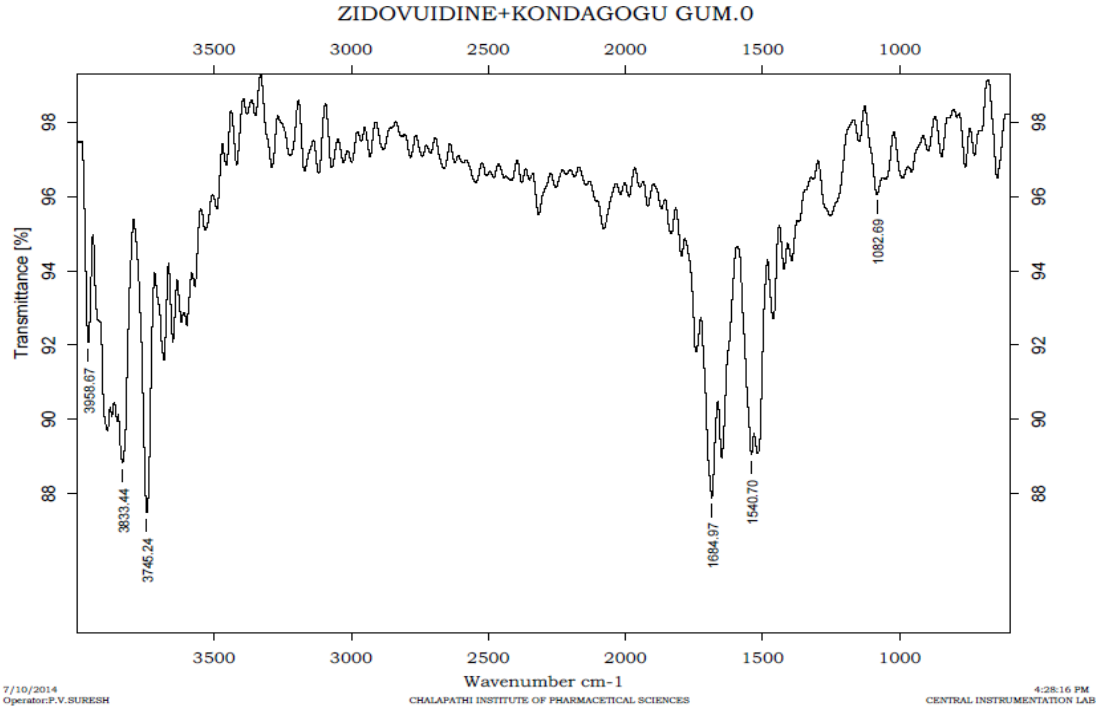


Figure 5: FT-IR spectra of the physical mixture (D+kondagogu gum)

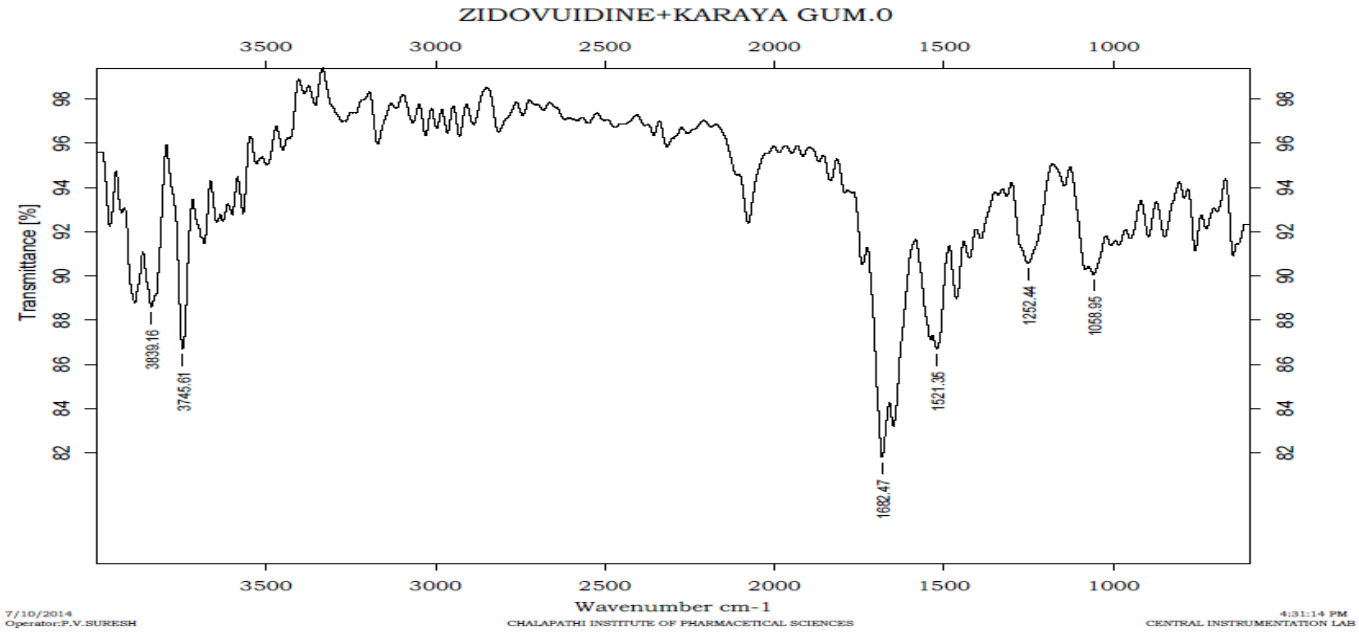


Figure 6: FT-IR spectra of the physical mixture (D+karaya gum)

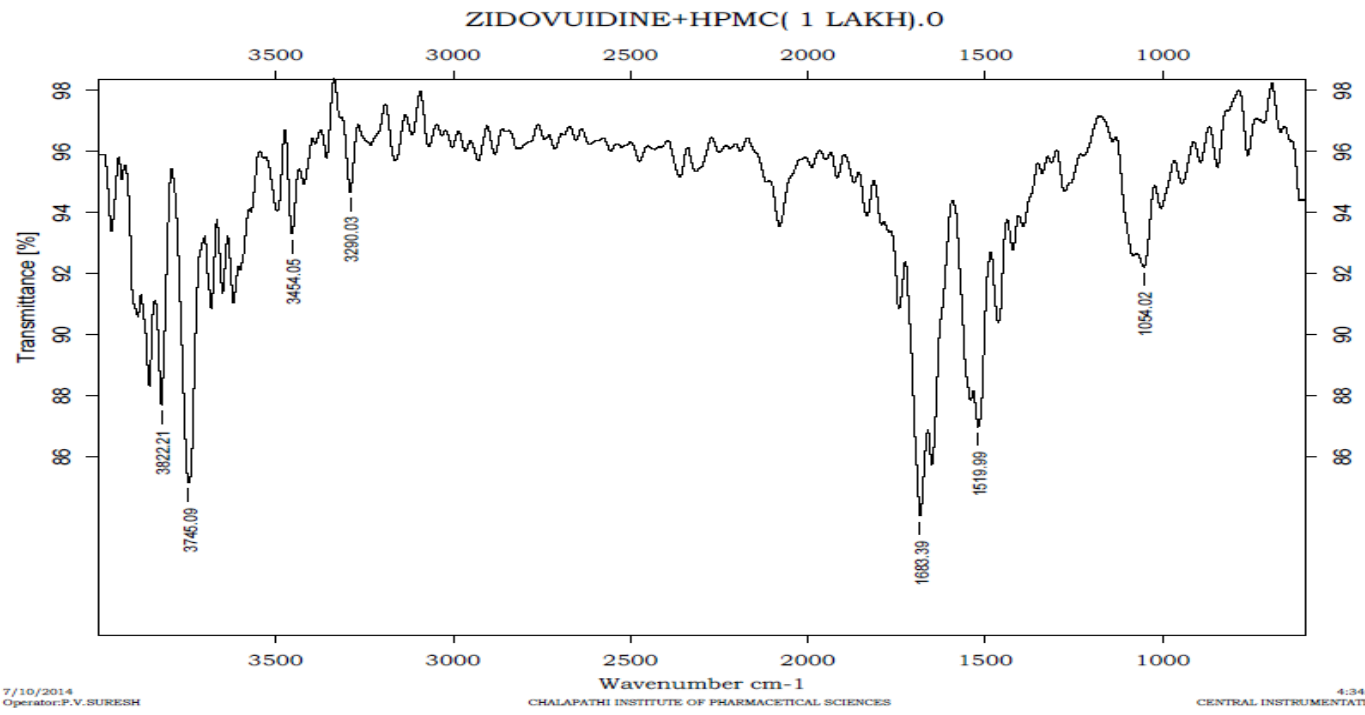


Figure 7: FT-IR spectra of the physical mixture (D+HPMCK100)

Similarity factor analysis: Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well as comparison of test formulations to the innovator release profile. The dissolution similarity was assessed using FDA recommended approaches. The similarity factor is a logarithmic, reciprocal square root transformation n of the sum of squared errors and it serves as a measure of the similarity of 2 respective dissolution profiles.

Table 10: f_2 factor values

Formulation code	F_2 factor
F1	39
F2	58
F3	64
F4	56
F5	66
F6	45
F7	58
F8	67
F9	70

Table 11: Mathematical modeling for drug release data obtained from zidovudine matrix tablet

Formula	Zero order		First order		Highuchi		Peppas			
	K_0	R^2	K_1	R^2	K_H	R^2	K	R^2	N	$t_{1/2}$
F1	15.17	0.987	0.428	0.978	120.1	0.996	43.451	0.976	0.422	0.988
F2	11.64	0.981	0.214	0.98	90.48	0.966	17.906	0.979	0.746	12.886
F3	9.368	0.988	0.168	0.983	83.43	0.970	10.375	0.976	0.921	16.08
F4	11.67	0.982	0.223	0.976	90.54	0.963	15.667	0.983	0.843	12.975
F5	9.283	0.987	0.20	0.996	84.65	0.969	11.246	0.996	0.931	3.465
F6	6.627	0.992	0.151	0.973	65.84	0.985	13.091	0.969	0.707	22.634
F7	11.61	0.981	0.237	0.995	93.02	0.96	12.531	0.986	0.999	2.924
F8	9.434	0.989	0.195	0.996	77.83	0.96	12.05	0.983	0.869	3.55
F9	7.598	0.989	0.2	0.972	75.79	0.97	12.387	0.993	0.838	19.742

	Weight variation	Hardness (Kg/cm^2)	Friability (%)	%Drug content
F1	498±0.01	5.93±0.23	0.43	96.5±1.501
F2	500.0.21	5.6±0.2	0.67	96.2±1.735
F3	503.0.19	5.93±0.23	0.82	99.5.±1.322
F4	499±0.05	6.33±0.11	0.48	98.8±1.616
F5	500±0.37	6.46±0.11	0.25	99.6±2.193
F6	498±0.42	6.4±0.2	0.36	97.8±1.014
F7	500±0.05	6.26±0.11	0.61	97.5±2.151
F8	500±0.02	5.93±0.23	0.54	99.9±1.882
F9		**5.86±0.11**	**0.39**	**98.6±1.442**

DISCUSSIONS

Zidovudine matrix tablets were prepared using three biodegradable polymers namely karayagum, kondagogu gum and HPMC (K100M). The aqueous medium on contact with polymer matrix gradually begins to hydrate from the periphery toward the centre, forming a

gelatinous swollen mass. The swelling of the tablets could be due to the hydration of the polymer too, which results in a rapid decrease in its glass transition temperature (T_g) to the temperature of the dissolution medium. Microscopically, there is a relaxation response of the polymer chains due to stresses introduced by the presence of the dissolution solvent. This results in an increase in the radius of gyration and end to end distances of the polymer chains, causing a significant increase in the molecular volume of the hydrated polymer. This reduces the free volume due to the presence of the micro pores, which may manifest itself as a shift in the drug release mechanism. The hydrated gel layer thickness determines the diffusional path length of the drug.

Drug - polymer compatibility studies

FT- IR of zidovudine was depicted in Figure No 6.12.FT-IR of zidovudine with karayagum was depicted in Figure No 6.15. FT-IR of zidovudine with Hupu gum was depicted in Figure No 6.13. FT-IR of zidovudine with HPMCK100m.

Physical characterization of the drug and polymers

Various physical parameters determined for the drug and polymers were listed in table. Melting point of the drug was found to meet the compendial requirements conforming that the drug is pure. Micromeritic properties revealed that both the drug and polymers have average flow ability i.e., 31.60 -36.56 indicating addition of glidant.

The standard graph of zidovudine (Table No 6) has shown good linearity with R^2 values 0.999and 0.998 in 0.1 N HCl and pH 6.8 buffer respectively, which suggests that it obeys the "Beer-Lambert's law".

Micromeritic properties of formulation blends

The micromeritic parameters of the formulation blends confirms good flow and packaging properties. Carr's index and Hausner's ratio were found to be in the range of 2.71- 13.98% and 1.02- 1.16. The results were given in table No 4.3.

5.4. Physical characterization of formulations

The results of the hardness, thickness, friability, and drug content of the tablets are given in Table No 20. The hardness of the tablets ranged from 6.26 to 7.6 kg/cm^2 and the friability values were less than 1.0% indicating that the matrix tablets were compact and hard. The thickness of the tablets depends on size of the punch and weight of the tablet and was between 3- 3.5mm. Drug content of the formulations was found to be 96.76to 102.64 % of zidovudine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Determination of swelling index

The swelling behavior indicates the rate at which the formulation absorbs water from the dissolution media and swells. The change in weight is characteristic of the water uptake and swelling.[75] The significant differences in weight gain were shown for matrices containing different gums and different proportions of the gums. Matrices containing a lower proportion of gum showed a lower degree of weight gain with time. This is expected since the lower proportion of gum would decrease the ability of the matrix to absorb water. The kondagogu gum matrix exhibited a high degree of swelling than other matrices. The results were given in Table No 6.8 and Figure No 6.9.

RELEASE KINETICS

To analyze the mechanism of drug release from the matrix tablets, the release data was fitted into various mathematical models. The correlation coefficients obtained for zero-order kinetics were found to be higher (0.949-0.998) when compared with those of first-order kinetics (0.884-0.969), indicating that the drug release from all the formulations followed zero-order kinetics.When the percent of zidovudine released from all formulations was fitted to the model developed by kors-meyer *et al* the mean diffusional exponent values (n) was found to be greater than 0.5 and less than 1 indicating that zidovudine release from matrices and zidovudine SR tablets followed Anomalous mechanism followed by swelling and relaxation of polymer chains.

CONCLUSION

A sustained release zidovudine matrix tablets with satisfactory release characteristic were successfully prepared by direct compression method using the selected hydrophilic polymers. Study indicated that increase in amount of the gums in the tablets resulted in a reduction in the release rate. The calculated release exponents (n values) and rate constants (K values) indicated the release behavior of all the formulations was case II transport mechanism with zero order kinetics except F5, F7,F8 formulation followed first order kinetics. It was concluded that Sterculia gum sustained for 10hrs. Hupu gum showed retardant for 12hours but 85% efficiency HPMC (K100M) showed for 12hrs retardant along with 96% efficiency. Among the three polymers HPMC(K100M) showed more satisfactory results compared to kondagogu gum gum, karaya gum.

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