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Design and Evaluation of Guar Gum Based Controlled Release Matrix Tablets of Zidovudine

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Abstract:
In the present investigation an attempt was made to formulate the oral controlled release zidovudine matrix tablets by using Guar gum as rate controlling polymer and to evaluate drug release parameters as per various release kinetic models. The tablets were prepared by wet granulation method. Granules were prepared and evaluated for loose bulk density, tapped density, compressibility index and angle of repose, shows satisfactory results. All the granules were lubricated and compressed using 12.6 mm flat faced punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, in vitro release studies and swelling index. All the formulations showed compliance with Pharmacopoeial standards. The in vitro dissolution study was carried out for 12 hours using paddle (USP type II) method in phosphate buffer (pH 6.8) as dissolution media. Formulation F-1 failed to sustain release beyond 10 hours. Among all the formulation, F-2 shows 95.97% of drug release at the end of 12 hours. Selected formulation (F-2) was subjected to stability studies for 3 months, which showed stability with respect to release pattern. Fitting the in vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Key-words: Zidovudine, Guar gum, Matrix tablets, Wet granulation, Controlled release

Introduction:

In recent years oral controlled delivery systems have gained increased importance and interest since it is necessary to improve the systemic absorption of the drugs and patient compliance. In addition, controlled delivery systems maintain uniform drug levels, reduce dose, side effects, and increase the safety margin. Matrix controlled release tablet formulations are the most fashionable and straightforward to formulate on a commercial scale. A wide variety of polymer matrix systems have been used in oral controlled drug delivery to obtain a desirable drug release profile, costeffectiveness, and broad regulatory acceptance.

In the systemic circulation, it is first converted into zidovudine triphosphate, which is pharmacologically active and prevents the replication of the HIV virus. The biological half-life of zidovudine triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Treatment of AIDS using conventional formulations of zidovudine is found to have many drawbacks such as adverse side effects due to accumulation of drug in multi-dose therapy,[1-2] poor patient compliance[3] and high cost. So, controlled release formulations of zidovudine can overcome some of these problems.

Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form.[4]Guar gum is galactomannan, obtained from the ground endosperm of the guar plant, Cyamopsis tetragonolobus. It has been investigated as controlled release carrier and regarded as nontoxic and nonirritant material.[5-7]

In this study, matrix tablets containing different concentrations of guar gum were prepared by wet granulation method and subjected to in vitro drug release studies to find the utility of guar gum in providing controlled release.

Materials and Methods:

Zidovudine was obtained from (Strides Arcolab, Bangalore). Guar gum and polyvinyl pyrrolidine (PVP-K-30) were procured from (Himedia laboratories Pvt. Ltd, Mumbai). Avicel pH 101 was purchased from (S.D. Fine Chemicals, Mumbai). Magnesium stearate and talc were obtained from (Loba Chemicals, Mumbai). All other ingredients used were of analytical grade.

Preparation of matrix tablets:

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given in Table 1. Zidovudine, Guar gum and Avicel pH 101 were mixed in a polybag, and the mixture was passed through mesh (No.60). Granulation was done using a solution of PVP- K-30 in sufficient isopropyl alcohol. The wet mass passed though mesh No.16. The wet granules were air dried for 2 hours. The granules were then sized by mesh No.22 and mixed with magnesium stearate and talc. Tablets were compressed at 600 mg weight on a 10-station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 12.6 mm flat-shaped punches. Six different formulas, having different concentrations of guar gum (10%, 15%, 20%, 25%, 30% and 35%), were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

Evaluation of granules:

The angle of repose was measured by using funnel method[8], which indicates the flowability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) [9] were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index[10] of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.The physical properties of granules were shown in Table 2.

Evaluation of tablets:

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods[11] shown in Table 3.

Drug content:

Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with pH 6.8 buffer and the solution was filtered through 0.45 µ membranes. The absorbance was measured at 266 nm after suitable dilution.

In-vitro drug release studies:

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer, maintained at 37 ± 0.5^0C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 266 nm. The study was performed in triplicate.

Drug release kinetics:

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug release vs time, first order (Equation 2) as log cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs square root of time.

$$C = K_0 t \ldots (1)$$

Where K_0 is the zero order rate constant expressed in units of concentration / time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.[12]

$$Log\ C = log\ C_0 - Kt/2.303 \ldots (2)$$

Where C_0 is the intial concentration of drug, k is the first order constant, and t is the time.[13]

$$Q = kt^{1/2} \ldots (3)$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.[14]

Mechanism of drug release:

To evaluate the mechanism of drug release from zidovudine controlled release tablets, data of drug release were plotted in korsmeyer et al's equation (Equation 4) as

Table 1: Tablet composition (%w/w) of different formulations of zidovudine controlled release matrix tablets

Ingredients	Formulation code					
	F1 F2		F3	F4 F5		F6
Zidovudine	50	50	50	50	50	50
Guar gum	10	15	20	25	30	35
PVP- K-30	5	5	5	5	5	5
Avicel pH 101	32	27	22	17	12	7
Magnesium stearate	2	2	2	2	2	2
Talc	1	1	1	1	1	1

Table 2: Granule properties of the different formulations of zidovudine controlled release matrix tablets

Parameters	Formulation Code					
	F1 F2		F3	F4	F5	F6
Angle of repose	25.46 ± 1.58	24.69 ± 1.54	27.14 ± 1.35	28.07 ± 1.41	29.39 ± 1.18	29.74 ± 1.33
Loose bulk density(LBD) (g/ml)	0.3464 ± 0.03	0.3702 ± 0.05	0.3655 ± 0.01	0.3241 ± 0.02	0.3863 ± 0.04	0.4312 ± 0.03
Tapped bulk density (TBD) (g/ml)	0.4276 ± 0.007	0.4081 ± 0.005	0.4396 ± 0.004	0.3859 ± 0.002	0.4796 ± 0.003	0.5194 ± 0.008
Compressibility index %	15.11 ± 0.16	13.63 ± 0.20	16.85 ± 0.44	16.00 ± 0.23	10.82 ± 0.48	16.92 ± 0.58

The values represent mean ± S.D; n=6.

log cumulative percentage of drug release vs log time and the exponent *n* was calculated through the slope of the straight line.

$$Mt/M\infty = kt^n \ldots (4)$$

Where $Mt/M\infty$ is the fractional solute release, *t* is the release time, *K* is a kinetic constant characteristics of the drug/polymer system, and *n* is an exponent that characterizes the mechanism of release of tracers.[15] For cylindrical matrix tablets, if the exponent n=0.45, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponents value of 0.89 is indicative of case-II Transport or typical zero-order release.[16]

Swelling behavior of controlled release matrix tablets:[17]

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation F-2, F-3 and F-6 was studied. One tablet from each formulation was kept in a Petridish containing pH 6.8 phosphate buffer. At the end of 1 hours, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 2 hours, weights of the tablet were noted, and the process was continued till the end of 12 hours. % weight gain by the tablet was calculated by formula; S.I = {(Mt-Mo) / Mo} X 100, where, S.I = swelling index, Mt = weight of tablet at time't' and Mo = weight of tablet at time t = 0.

Table 3: Tablet properties of the different formulations of zidovudine controlled release matrix tablets

Parameters	Formulation code					
	F1 F2		F3	F4	F5	F6
Thickness (mm)	4.25 ± 0.01	4.18 ± 0.02	4.30 ± 0.02	4.34 ± 0.01	4.21 ± 0.04	4.17 ± 0.07
Hardness (kg/cm^2)	6.8 ± 0.15	7.0 ± 0.20	6.2 ± 0.30	6.6 ± 0.18	6.9 ± 0.05	6.3 ± 0.10
Friability (%)	0.25	0.28	0.34	0.42	0.44	0.50
Drug content (%)	99.91 ± 0.31	99.19 ± 0.19	99.08 ± 0.34	99.62 ± 0.45	99.78 ± 0.13	98.92 ± 0.27

The values represent mean ± S.D; n=6.

Table 4: Kinetic values obtained from different plots of formulations, (F1 to F6)

Formulation code	Higuchi's plots[1]	Korsmeyer et al's plots[2]		First-order plots[3]	Zero-order plots[4]
	R^2 Slo	pe(n)	R^2	R^2	R^2
F1	0.998	0.4479	0.995	0.870	0.901
F2	0.995	0.6462	0.998	0.901	0.972
F3	0.993	0.6925	0.994	0.996	0.975
F4	0.992	0.7194	0.991	0.997	0.979
F5	0.985	0.7970	0.996	0.998	0.997
F6	0.971	0.8672	0.995	0.999	0.998

[1]Higuchi equation, Q = Kt½.; [2]Korsmeyer et al's equation, Mt/ M∞=Kt^n.; [3]First order equation, Log C = log C_0 - Kt/2.303.; [4]Zero order equation, C=K_0 t.

Results and Discussion:

Granulation is the key process in the production of many dosage forms. To ensure good content uniformity and avoid flow related intertablet weight variation problems, wet granulation is preferred in routine commercial production. Wet granulation was thus used in the present study. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics and size can significantly affect the rate of dissolution of drug contained in a formulation. The granules of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, and compressibility index. The results of angle of repose and compressibility index (%) ranged from (24.69 ± 1.54 to 29.74 ± 1.33) and (10.82 ± 0.48 to 16.92 ± 0.58), respectively. The results of loose bulk density and tapped bulk density ranged from (0.3241 ± 0.02 to 0.4312 ± 0.03 and 0.3859 ± 0.002 to 0.5194 ± 0.008), respectively. The results of angle of repose (<30) indicate good flow properties of granules.[18,19] This was further supported by lower compressibility index values[18] (Table 2). The physical properties of different batches of developed matrix tablets are given in (Table 3). The thickness of the tablets ranged from (4.17 ± 0.07 to 4.34 ± 0.01) mm. All the batches showed uniform thickness.

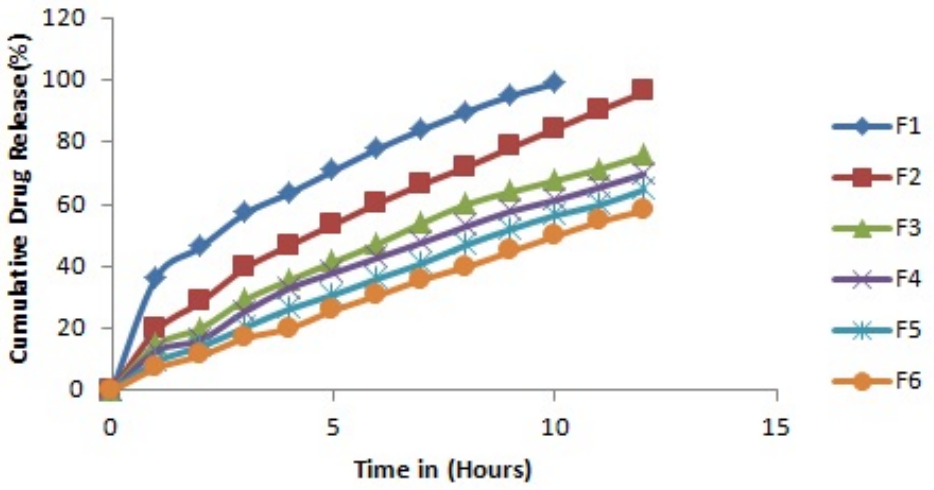
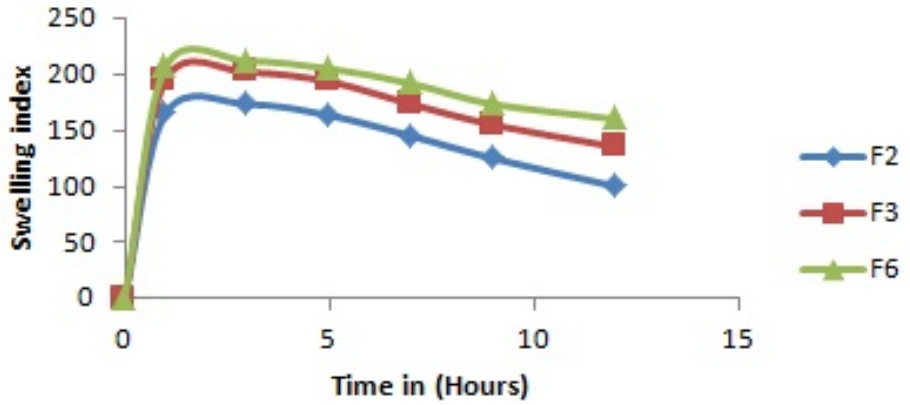


Figure 1: In-vitro dissolution profile of F1 to F6 formulations.



Relationship between swelling index and time of formulation F2 (-◊-) F3 (-■-) F6(-▲-)

Figure 2: Relationship between swelling index and time.

The average percentage deviation of 20 tablets of each formulation was less than (5%), and hence all formulations passed the test for uniformity of weight as per official requirements (Pharmacopoeia of India 1996). The hardness of the tablets of all the formulations ranged from (6.2 $\pm$ 0.30 to 7.0 $\pm$ 0.20)kg/cm^2. Tablets hardness is, however, not an absolute indicator of strength. The percentage friability of the tablets of all the formulations ranged from (0.25% to 0.50%). In the present study, the percentage friability for all for formulations was below 1% w/w, indicating that the friability is within the prescribed limits (Banker and Anderson 1987). Drug content was found to be uniform among different formulations of the tablets and ranged from (98.92 $\pm$ 0.27 to 99.91 $\pm$ 0.31). The results of the dissolution studies for formulations F-1, F-2, F-3, F-4, F-5, F-6 are shown in the Figure 1.

The cumulative percentage drug release for F-1, F-2, F-3, F-4, F-5 and F-6 was (98.91%, 95.97%, 75.65%, 69.68%, 64.62% and 57.88%) at the end of 12 hours respectively. Formulation F1 failed to sustain release beyond 10 hours. Among all the formulation, F2 shows 95.97% release at the end of 12 hours. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration.

The swelling index was calculated with respect to time (Figure 2). As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to 3 hours. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration, and as gum concentration increases, swelling index was increased. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of guar gum.

The inverse relationship was noted between amount of gum and release rate of zidovudine. Increasing the amount of gum in the formulation from 10 %w/w to 35 %w/w, resulted in slower rate, and decreased amount of drug release from the tablet Figure 2. This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix, where hydration of individual guar gum particles results in extensive swelling. Thus, maintain the integrity of the tablets, and retarding further penetration of the dissolution medium, prolonged the drug release.[3] The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of the drug release (Table 4).

Drug release data of formulation F-1 shows good fit into the Higuchi equation (R^2=0.998) with slope (n) value 0.4479 indicating that diffusion was the predominant mechanism of drug release from this formulation. When the data were plotted according to Korsmeyer-Peppas equation, the formulations (F-2 to F-6) showed high linearity (R^2=0.998,0.994, 0.991, 0.996, and 0.995) with a comparatively high slope (n) values of > 0.5 which appears to indicate a coupling of diffusion and erosion mechanisms–so called anomalous diffusion. Hence, diffusion coupled with erosion might be the mechanism for the drug release from Guar gum based matrix tablets.

Conclusion:

From the above observations it is concluded that slow and controlled release of zidovudine over a period of 12 hours was obtained from matrix tablets (F-2 to F-6). Use of natural hydrophilic polymer like guar gum was successful in the formation of matrix and at the same time it is effective in retarding the drug release. Among all the formulation, F-2 shows that 95.97% of drug release at the end of 12 hours. The cumulative percentage drug was decreased by increase in polymer concentration. The mechanism of drug was diffusion coupled with erosion. The stability studies show that there was no significant change in hardness, friability, and drug content of selected formulation F-2. The controlled and efficient drug delivery system developed in the present study will maintain plasma zidovudine levels better, which will overcome the drawbacks associated with the conventional therapy.

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