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FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF LAMIVUDINE

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ABSTRACT

An ideal drug delivery system should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. Hence, the DDS should deliver the drug at a rate dictated by the needs of the body over the period of treatment. An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take in to account the site specific absorption rates within the gastrointestinal tract (GIT). Therefore, there is a need of developing drug delivery system that release the drug at the right time, at the specific site and with the desired rate. Matrix system was the earliest oral extended release platform for medicinal use. The current study focuses on the use of tamarind seed polysaccharide (TSP) as an excipient in medication delivery systems. The planned work's major goal is to concentrate on the industrial applications of this polysaccharide, with a special focus on its physical and chemical characteristics for the development of novel drug delivery methods. This goal drives the development of novel synthetic excipients that take advantage of the current limitations in terms of toxicity, compatibility, and cost effectiveness. In this work, we attempted to take use of TSP's advantages for Lamivudine oral delivery. An attempt was made to construct and describe Lamivudine sustained release matrix tablets for HIV therapy utilizing a mix of TSP and ethylcellulose. These results show that all matrix tablet formulations release the drug in a sustained manner for up to 24 hours, but formulation F2 released 98.82 percent of the drug and the release was found to be extended for up to 24 hours, indicating that the formulation could be used as a once daily sustained release matrix tablet of Lamivudine. The formulation's characteristics and test requirements were both satisfactory.

Key words: TSP, Lamivudine, HIV, Sustained Release, Matrix Tablets.

INTRODUCTION:

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance (Kumar et al., 2012). Approximately 50% of the drug products available in the market are administered orally and historically, oral drug administration has been the predominant route for drug delivery (Aher et al., 2011; Shivakumar et al., 2004). Tablets are the most commonly and widely used dosage form. This type of drug delivery system is called conventional drug delivery system and is known to provide an immediate release of drug. Such immediate release products results in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. An alternative to administration of another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations In recent years, pharmaceutical industries and academic laboratories have been focused on establishment of novel drug delivery system/modified release/sustained release or the controlled-release drug delivery system rather investigation and development of new drug due to investigation cost of a new drug (Sharma et al., 2009; Chien, 2002; Bhosale et al., 2000; Allen et al., 2005).

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different release mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile

comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's in a narrow range, above the minimum effective level and below toxic level. This type of sustained-release tablet has clearly shown the potential of the tablet as a reliable sustained release dosage form with good release profile precision (Moji and Harry, 2008). Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression (Patel et al., 2011; Allen et al., 2013; Chein, 1992; Remington, 2002, Martin, 2006). The goal of this study is to use tamarind seed polysaccharide (TSP) as an excipient in medication delivery systems. The planned work's major goal is to concentrate on the industrial applications of this polysaccharide, with a special focus on its physical and chemical characteristics for the development of novel drug delivery methods. This goal drives the development of novel synthetic excipients that take advantage of the current limitations in terms of toxicity, compatibility, and cost effectiveness. Lamivudine is a powerful antiviral drug used to treat AIDS. Treatment of AIDS with Lamivudine in its traditional formulation has a number of disadvantages, including severe side effects from drug buildup during multidose therapy, low patient compliance, and a high cost. Lamivudine in a sustained and controlled release formulation might potentially address the drawbacks of current methods.

Tamarind seed polysaccharides are a polysaccharide polymer (D-galactose, D-xylose, and D-glucose) derived from the endosperm of seed kernels that has a wide range of uses in drug delivery systems. Polysaccharides are a preferred substance because of its low toxicity, biodegradability, lack of carcinogenicity, and regulatory approval. The new dosage form has the potential to release the medication over a longer period of time, improving absorption and bioavailability and so providing more

therapeutic effect for HIV therapy. As the frequency of dosage administration reduces, patient compliance improves with Lamivudine's sustained release matrix tablet. In addition, the total dose of the medicine may be reduced, which may minimize the drug's dose-dependent adverse effects and lower the overall cost of the formulation.

MATERIAL AND METHOD

Material

Tamarindus indica seeds were used to extract the tamarind seed polysaccharide collected from Vindhya herbal Bhopal. Levofloxacin was received as a gift sample from Pharmaceutical Company. All other solvents and reagents were purchased from Merck (Germany) and were of analytical grade.

Methods

Isolation of Tamarind Seed Polysaccharide (TSP)

The TSP was made according to the procedure described by Rao et al (1973). A slurry was made by mixing 20g of tamarind kernel powder with 200ml of cold distilled water. The slurry was put into 800ml of boiling distilled water in a quick manner. In a water bath, the solution was cooked for 20 minutes with constant stirring. The resulting thin, clear solution was left overnight to settle out the majority of the proteins and fibers. The solution was then centrifuged for 20 minutes at 5000 rpm. By continuously swirling, the supernatant was separated and put into twice the volume of 100% ethanol. The product was sandwiched between two layers of felt. The precipitate was washed in 100% ethanol, isopropanol, and methanol before being dried in a freeze dryer at -50-60°C. The dry material was crushed and sieved to create granules in a variety of particle sizes, which were then utilized to make tablets (Saikia et al., 2017).

Preparation of matrix tablet of lamivudine

Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The hydrophilic polymer selected here is tamarind seed polysaccharide. This polymer provides pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms. However the use of hydrophilic matrix alone for extending 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 become essential to include hydrophobic polymers in the matrix system (Arkhel et al., 2011; Das et al., 2017). Hence, in the present work, an attempt has been made to formulate the extended-release

matrix tablets of lamivudine using hydrophilic matrix material (tamarind seed polysaccharide) in combination with hydrophobic ethylcellulose.

Formulation of Matrix Tablet of Lamivudine

Matrix tablets were prepared by direct compression method. The ingredients as given in table 1 and 2 were mixed in gometric dilution principle and were blended in a polybag. The blend was compressed using twelve station rotatory tablet punching machine (RIMEK) using 11.5 mm standard concave punches.

Table 1 Composition of matrix tablets of lamivudine using different ratio of TSP

Formulation Code	Drug (mg)	TSP (mg)	MCC (mg)	Magnesium Sterate (mg)
T1	200	100	294	6
T2	200	200	194	6
T3	200	300	94	6

Table 2 Formulation design for sustained release matrix tablets of lamivudine

Formulation Code	Lamivudine (mg)	TSP (mg)	HPMCK100M (mg)	MCC (mg)	Magnesium Sterate (mg)	Talc
F1	200	100	100	194	5	1
F2	200	150	100	144	5	1
F3	200	200	100	94	5	1
F4	200	250	100	44	5	1
F5	200	150	100	144	5	1
F6	200	100	200	94	5	1
F7	200	50	200	144	5	1
F8	200	100	200	94	5	1

Evaluation of matrix tablets of Lamivudine

Weight Variation

20 tablets from each composition were weighed individually and average weight was calculated. Then the individual tablet weight was compared with the average tablet weight (Aulton, 1998; Chang and Robinson, 1990). The weight variation limits as per IP 1996 are as follows:-

Standards for weight variation (IP 1996)

S. No.	Average weight of tablet	Maximum percentage variation allowed
1	80mg or less	10
2	80 to 250 mg	7.5
3	250 mg or more	5

Hardness

The tablet was placed between two anvils of hardness tester (Monsanto) and increasing amount of force (kg) was applied. The reading at the marked scale was recorded for the pressure which is required to break the tablet.

Friability

Ten tablets was weighed and was placed in the rotating disc of Roche friabilator. This apparatus was operatedfor 4 minutes at 25 rpm. The tablet was then collected, dedusted and weight again. The % friability was calculated based on weight loss after the test.

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

Drug Content

Five tablets fom each batch was taken and was triturated. Powder equivallent to 100mg of drug was weighed and was transferred to volumetric flask and to it distilled water was added and it was then shaken for 5 minutes and finally distilled water was added to make the volume up to 100ml and solution was then sonicated for 5 minutes and filtered through Whatman filter paper. Finally a solution of 15µg/ml was prepared and absorbance was measured at 270nm using UV spectrophotometer (Shimadzu 1700) against blank (Hadjiioannou et al., 1993; Bourne, 2002).

***In vitro* Drug Release**

In vitro drug release studies of the prepared matrix tablets were conducted for a period of

24 hours using USP II dissolution tester apparatus (Electrolab-TDT-08L) at 37 ± 0.5 C and 50 rpm speed using 900ml phosphate buffer pH 6.8 as dissolution media. The dissolution study was carried out under sink condition. At appropriate time an interval sample were withdrawn from dissolution media and was replaced with fresh media to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analysed by UV spectrophotometer. The amount of drug present in the sample was then calculated; from this the cumulative percentage release was calculated.

RESULTS AND DISCUSSION

Sustained release tablet formulations are recommended for this kind of therapy because they improve patient compliance, maintain consistent drug levels, minimize dosage and adverse effects, and enhance the safety margin for high-potency medicines. In light of these issues, we attempted to use the benefit of TSP for Lamivudine oral delivery in the current study. In this study, an attempt was made to create and describe a sustained release matrix tablet of Lamivudine for HIV therapy utilizing a combination of TSP and ethylcellulose.

The current study focuses on the use of tamarind seed polysaccharide (TSP) as an excipient in medication delivery systems. The planned work's major goal is to concentrate on the industrial applications of this polysaccharide, with a special focus on its physical and chemical characteristics for the development of novel drug delivery methods. This goal drives the development of novel synthetic excipients that take advantage of the current limitations in terms of toxicity, compatibility, and cost effectiveness.

When creating an oral sustained-release formulation, hydrophilic matrices are an intriguing alternative. They can be used to deliver both water-soluble and water-insoluble medicines in a regulated manner. In this work, we attempted to take use of TSP's advantages for Lamivudine oral delivery. An attempt was made to construct and describe Lamivudine sustained release matrix tablets for HIV therapy utilizing a mix of TSP and ethylcellulose.

Table depicts the various data treatment strategies. These results show that all matrix tablet formulations release the drug in a sustained manner for up to 24 hours, but formulation F2 released 98.82 percent of the drug and the release was found to be extended for up to 24 hours, indicating that the formulation could be used as a once daily sustained release matrix tablet of Lamivudine.

Table 3 Comparision of yields of tamarind seed polysaccharide (TSP)

S. No.	Precipitating Agent	Quantity of TKP (gm)	Quantity of TSP (gm)	% Yield
1	Absolute ethanol	20	11.8	59
2	Iso-propanol	20	10.8	54
3	Methanol	20	9.4	47

Table 4 *In vitro* release profile for matrix tablets of lamivudine using TSP

S. No.	**Time (hours)**	**Cumulative % drug released**		
		Formulation T1	**Formulation T2**	**Formulation T3**
1	1	42.47	40.54	39.38
2	2	65.66	57.81	53.45
3	3	79.51	71.34	65.34
4	4	88.12	78.89	73.32
5	5	93.57	83.41	78.84
6	6	95.12	87.42	82.86
7	7	97.54	91.42	87.72
8	8	99.84	96.48	93.21

Table 5 Evaluation parameter for matrix tablet of lamivudine

S. No.	**Formulation Code**	**Weight Variation**	**Hardness (kg/cm^3)**	**% Friability**	**% Drug content**
1	F1	588 ±2 %	8	0.8	97.19
2	F2	582 ±3 %	8.67	0.74	98.23
3	F3	603 ±0.5%	9	0.69	96.98
4	F4	584 ±2.67%	9.17	0.62	97.72
5	F5	575 ±4.17%	9.5	0.58	99.86
6	F6	608 ±1.33%	10	0.59	98.04
7	F7	579 ±3.5 %	9.5	0.63	97.33
8	F8	587±2.17%	8.83	0.57	98.67

Table 6 Release profile of drug from matrix tablet of lamivudine (formulation F2)

S. No.	Time (T) (hrs)	Root T	Log T	Cumulative % drug		Log Cumulative % drug	
				Released	Retained	Released	Retained
1	1	1	0	39.87	60.13	1.60	1.78
2	2	1.414	0.301	49.79	50.21	1.697	1.70
3	3	1.732	0.477	53.69	46.31	1.73	1.67
4	4	2	0.602	57.87	42.13	1.76	1.62
5	5	2.236	0.699	60.71	39.29	1.78	1.59
6	6	2.449	0.778	63.83	36.17	1.81	1.56
7	7	2.646	0.845	67.48	32.52	1.83	1.51
8	8	2.828	0.903	70.79	29.21	1.85	1.47
9	10	3.162	1	74.25	25.75	1.87	1.41
10	12	3.464	1.079	78.29	21.71	1.89	1.34
11	15	3.873	1.176	84.98	15.02	1.93	1.18
12	18	4.243	1.255	90.84	9.16	1.96	0.96
13	21	4.583	1.322	95.53	4.47	1.98	0.65
14	24	4.899	1.380	98.82	1.18	1.99	0.072

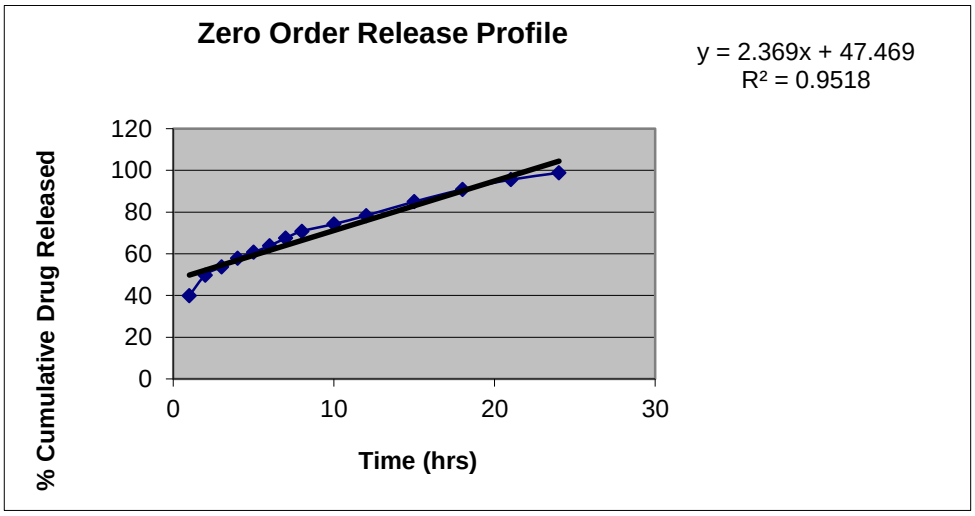

Figure 1: *In vitro* drug release of lamivudine from formulatiom F2 (Zero order kinetics)

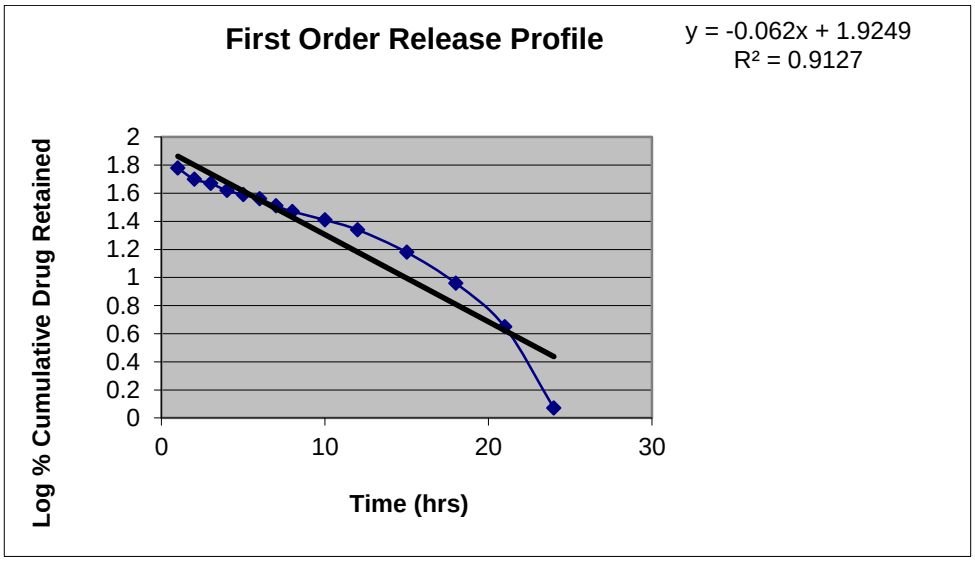

Figure 2: *In vitro* drug release of lamivudine from formulatiom F2 (First order kinetics)

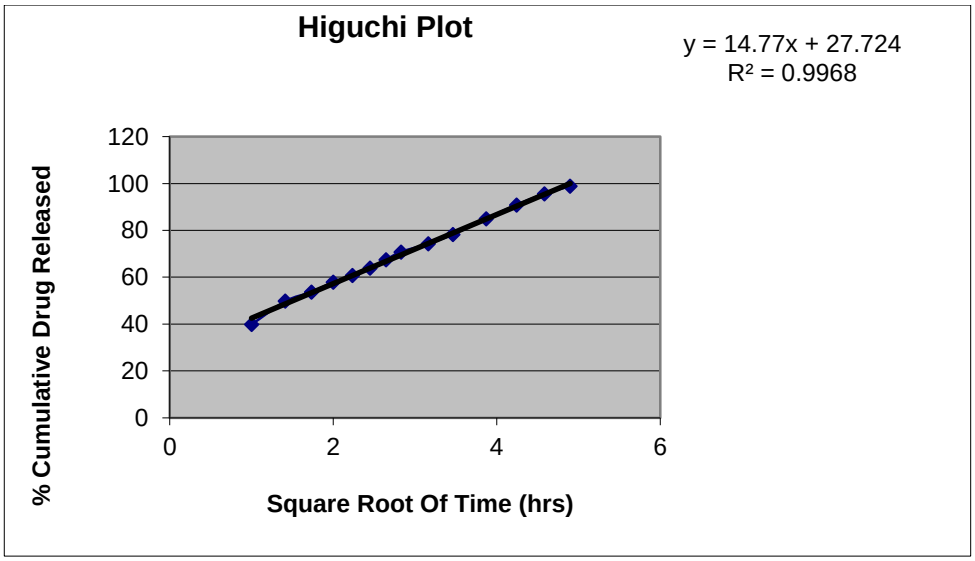

Figure 3: *In vitro* drug release of lamivudine from formulatiom F2 (Higuchi's classical diffusion equation)

CONCLUSION

Drug release kinetics revealed that Higuchi's equation best characterized the drug release pattern, as the plots exhibited the maximum linearity (r = 0.9968), although zero-order kinetics also showed a close connection (r =0.9518). As a result, it was discovered to be a better combination for the formulation of

Lamivudine sustained release matrix tablets. The research might be expanded to include a stability analysis and an in vivo profile of formulations. The formulation's pharmacotechnical characteristics and test requirements were both satisfactory.

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