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IN VITRO RELEASE STUDIES OF DEVELOPED TADALAFIL MOUTH DISSOLVING TABLETS

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ABSTRACT
For industrially manufactured pharmaceutical dosage forms, product quality tests and performance tests are required to ascertain the quality of the final product. Current compendial requirements specify a disintegration and/or a dissolution test to check the quality of oral solid dosage forms. The release rate of Mouth dissolving tablets of selected drug tadalafil was determined using USP dissolution testing apparatus II (Electro lab, India). The dissolution testing was performed using 900ml of phosphate buffer pH 6.8 at 37±0.5°C temperature and speed 50 rpm. Sample of 05ml was withdrawn at 02 minutes interval of time upto 20 minutes. The drug releases from these tablets were found to increase with increase in the concentration of disintegrant used in the formulation. Thus, it can be concluded that *in vitro* release of drugs is a direct function of its solubility in the dissolution medium. When plotted according to Peppas equation, formulation F6 for tadalafil showed good linearity (r^2=0.988), with a slope (n) value of 0.364 respectively. This probably indicates that the drug release of tadalafil is by Non-Fickian diffusion, when the tablet enters an *in vitro* dissolution medium, drug particles initially pass into solution from the surface (immediate release). The *in vitro* drug release profiles were plotted according to zero order, first order, Higuchi and Peppas equations to understand the mechanism of drug release and to compare the differences in the release profile of various batches of tadalafil tablets.

KEYWORDS: Tadalafil, Higuchi and Peppas.

INTRODUCTION
The oral route is the most preferred route of administration of dosage forms, due to its potential advantages like ease of administration, convenient dosing, self-medication, no pain and patient compliance. Hence tablets and capsules are the most popular dosage forms[1], but the important drawback of these dosage forms is dysplasia[2] which can be solved by developing orally disintegrating / dissolving tablet (ODT), which disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing.[3] In pharmaceutical sciences, disintegration usually means the process by which a solid dosage form breaks up, when it comes in contact with aqueous medium and thus promotes the rapid release of drug for faster absorption and good bioavailability.[4,5,6] United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which isintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute. ODT's are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapidmelts.[7,8] In the present work Tadalafil (figure:01) was used as drug which appear in white crystalline powder with molecular weight of 389.40 g/mol having very good specific Type V phosphodiesterase inhibitor activity. Through the inhibition on PDE-V, lead to increased concentrations of cGMP, producing smooth muscle relaxation and increased blood flow to the corpus cavern sum, thereby enhancing erectile response following appropriate sexual stimulation, but it was very poorly insoluble drug and shows poor absorption. By taking the account of poor solubility of Tadalafil, work was planned to formulate and evaluate fast disintegrating tablets in order to ensure increased bioavailability, due to rapid disintegration and dissolution of Tadalafil fast disintegrating tablets. MDT will avoid missing out of dose even during traveling or other situations where there is no access to water. The present investigation deals with the development of an effective and stable MDT of oxcarbazepine having adequate hardness, low disintegration time and pleasant taste.[9,10]

MATERIAL AND METHOD

Dissolution Studies

The release rate of Mouth dissolving tablets of selected drug tadalafil was determined using USP dissolution testing apparatus II (Electro lab, India). The dissolution testing was performed using 900ml of phosphate buffer pH 6.8 at 37±0.5°C temperature and speed 50 rpm. Sample of 05ml was withdrawn at 02 minutes interval of time upto 20 minutes and replaced with fresh medium to maintain sink condition and the percentage of drug release was determined using HPLC.[11]

Kinetics study

Kinetics of drug release is studied by plotting the data obtained from *in vitro* release in various kinetics models.

Zero Order Kinetics: The graph was plotted as cumulative % drug release Vs Time where the drug release rate is independent of its concentration.

$$C = K_0 t$$

Where, K_0 = Zero order rate constant expressed in units of concentration/time
t = Time in hours.

First order Kinetic model: The graph was plotted as log cumulative % of drug remaining Vs Time, where release rate is concentration dependent

$$\text{Log } C = \log C_0 - K_t / 2.3030$$

Where, C0 = Initial concentration of drug
K = First order constant
t = Time in hours.

Higuchi kinetics

Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The graph was plotted as cumulative % drug released Vs square root of time.[12]

$$Q = Kt_{1/2}$$

Where, K = Constant reflection design variable system
$t_{1/2}$ = Time in hours.

Hence, drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one then the particular dosage form is considered to follow Higuchi kinetics of drug release.

Hixson-Crowell erosion equation: It describes the drug release with changes in the surface area and the diameter of particles the data were plotted using the Hixson and Crowell rate equation. The graph was plotted by cube root of % drug remaining in matrix Vs time.[13]

Q0
1/3 – Qt
1/3 = KHC t.

Where, Qt = Amount of drug released in time t
Q0 = Initial amount of drug in tablet.
KHC = Rate constant for Hixon crowell rate equation

Korsmeyer-Peppas equation: To find out the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs log time.

$$Mt / M\alpha = Kt^n,$$
$$\text{Log } Mt / M\alpha = \log K + n \log t$$

Where, Mt / Mα = Fraction of drug released at time t
K = Kinetic rate constant
t = Release time
n = Diffusion exponent indicative of the mechanism drug release.

This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log Time.[14]

Optimization of mouth dissolving Tablets of Tadalafil by Taguchi Method

The Taguchi experimental design was selected to investigate the effect of different parameters on the mean and variance of the process performance and to obtain an optimal, well-functioning process.[15] The parameter of the taguchi design generally includes the following steps: (1) identifying the objective of the experiment; (2) identifying the quality characteristic (Performance measure) and its measurement systems; (3) determining the factors that may influence the quality characteristic and their levels; (4) selecting the appropriate orthogonal arrays (OA) and assigning the factors at their levels to the OA; (5) conducting the test described by the trials in the OA; (6) analysing the experimental data using the analysis of variance (ANOVA) to evaluate which factors are statistically significant and finding the optimum levels of factors and (7) verifying the optimal design parameters through confirmation experiment.

The Taguchi method uses a statistical measure of performance called signal-to-noise (*S*/*N*) ratio, which was used in this work to evaluate the quality of results. Both mean and variability are taken into account while calculating the S/N ratio. The S/N ratios are different according to the type of characteristic. In this design, orthogonal arrays arrange the affecting parameters and their levels in the way, most likely to affect the process. Unlike factorial design, where all the possible combinations are tested, taguchi employs a minimal number of trials by testing pairs of combinations. Normally, in the case of eight factors with two levels, 2^8 = 256 experiments should be conducted. According to the taguchi method, the standard orthogonal array, namely L4 that reduces the number of experiments to eight was used. The designed L4 is an array of eight experiments with the specified combination of levels. This saves both time and resources. The optimal parameters obtained from these trials are insensitive to environmental changes and other noise factors.[15,16]

Four experimental trials (Table) involving three independent variables at higher and lower levels were generated using Design-Expert® (Version 9; Stat-Ease, Inc, USA).

Select	Std	Run	Factor 1 A:A	Factor 2 B:B	Factor 3 C:C	Response 1 R1	Response 2 R2
	4	1	2	2	1	7	99.8
	1	2	1	1	1	15	90.3
	2	3	1	2	2	12	92.3
	3	4	2	1	2	11	97

Factor A: Amount of Spray Dried Lactose + Crospovidone.
Factor B: Amount of Mannitol + Crospovidone.
Factor C: Amount of MCC Ph102 + Crospovidone.
R1: Disintegration Time (Sec).
R2: Drug Release in 5 Mins (Q_5).

RESULT AND DISCUSSION

In vitro release studies of developed tadalafil mouth dissolving tablets

Table. 1: Cumulative % drug release of trial batches.

Time (Min)	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	15.58	17.58	27.65	32.50	30.25	30.72
2	29.58	40.25	35.02	53.25	46.58	43.05
3	44.58	59.33	48.51	61.25	60.25	68.80
4	59.80	69.58	64.25	71.56	72.65	80.26
5	68.90	78.60	85.60	86.50	82.65	94.58
10	75.60	87.14	95.04	95.60	98.57	99.99

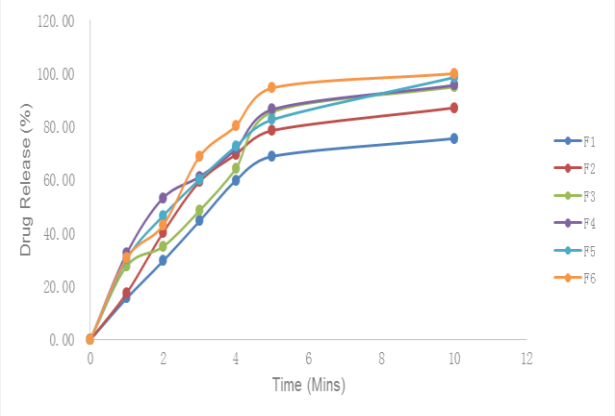

Figure. 2: *In vitro* dissolution profile of formulation.

A suitable *in vitro* dissolution method serves as a valuable quality control tool to assess batch to batch release performance and to assure the physiological availability of the drug. The *in vitro* dissolution test is also used to guide formulation development and to monitor manufacturing processes. As a regulatory test, it is used to approve minor changes in formulation, changes in the site of manufacturing and also to assess the scale up of the bio-batch to the production batch. All the batches have shown that as the disintegrant concentration increases. The drug release rates for tadalafil mouth dissolving tablets were shown in Table 1 and Figure 1. However, the drug releases from these tablets were found to increase with increase in the concentration of disintegrant used in the formulation. Thus, it can be concluded that *in vitro* release of drugs is a direct function of its solubility in the dissolution medium.

Kinetics and mechanism of drug release

Table. 2: Regression coefficient (r^2) values of release from different kinetic.

Formulation	Zero order r^2	First order r^2	Higuchi Model r^2	Korsmeyer model r^2	Hixson-Crowel r^2	Cube root r^2
F1	0.970	0.965	0.939	0.843	0.948	0.967
F2	0.981	0.977	0.961	0.658	0.965	0.979
F3	0.987	0.979	0.966	0.662	0.977	0.986
F4	0.994	0.993	0.987	0.686	0.993	0.994
F5	0.975	0.970	0.944	0.648	0.952	0.971
F6	0.989	0.985	0.990	0.364	0.988	0.986

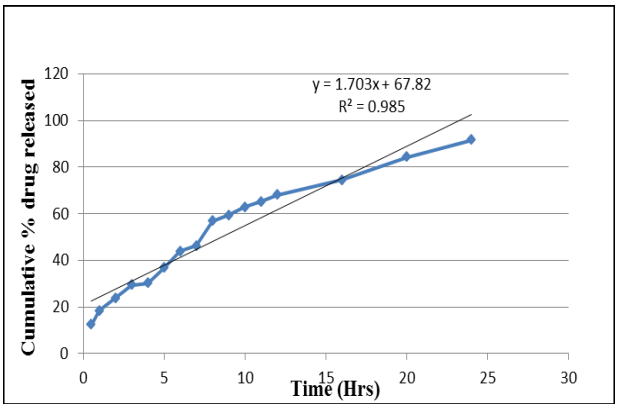

Fig. 3: Zero order plot of *in vitro* drug release data.

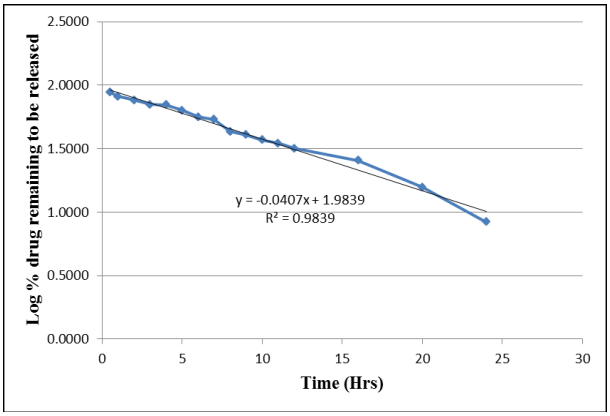

Fig. 4: First order plots of *in vitro* drug release data.

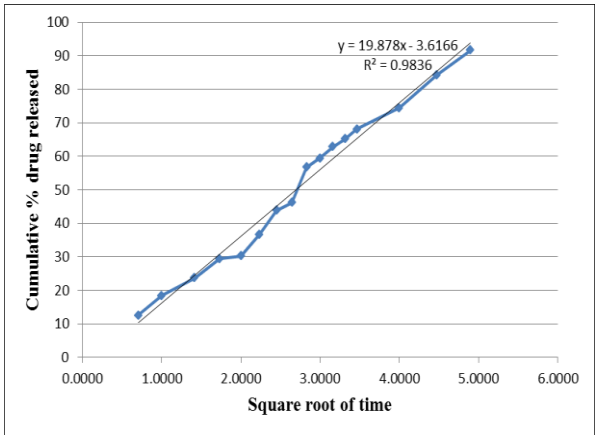

Fig. 5: Higuchi plots of *in vitro* drug release data.

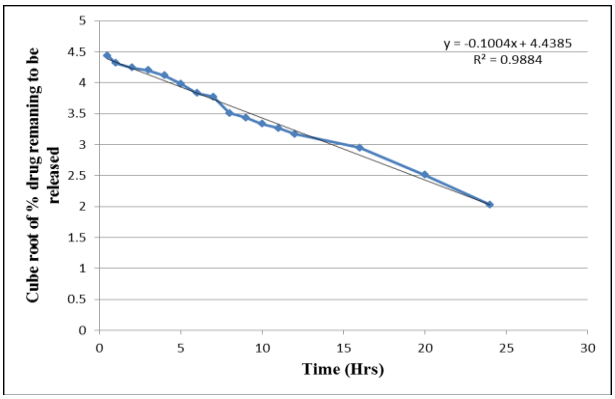

Fig. 6: Hixson Crowell plot of *in vitro* drug release data.

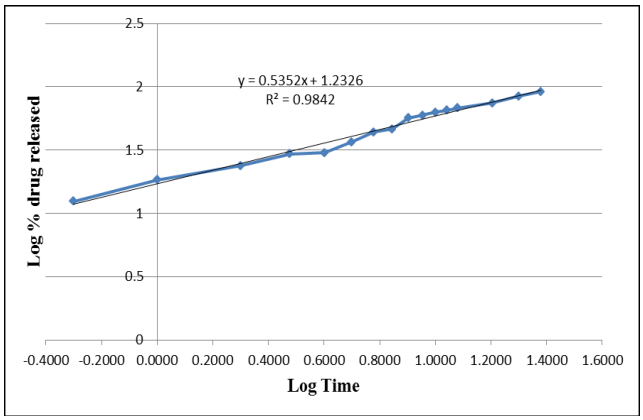

Fig. 7: Korsmeyer-Peppas plot of *in vitro* drug release data.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: such as zero order (cumulative percentage of drug release versus time) (equation 1), first order (log cumulative percentage remaining to release versus time) (equation 2), Higuchi (cumulative percentage of drug released versus square root of time) (equation 3) and Peppas (log cumulative percentage of drug release vs log time) (equation 4).

$Qt = k0\ t$ (1)

Where, 'Q' is the amount of drug release in time 't' and 'K0' is the zero - order rate constant and 't' is the time in hours.

$\ln Qt = \ln Q0 - k_1.\ t$ (2)

Where,'Q0' is the initial concentration of drug and 'k1' is the first order rate constant.

Qt = K_2 $t_{1/2}$ (3) Where, 'K_2' is the rate constant of Higuchi equation106. Hence, drug release rate is proportional to the reciprocal of the square root of time. The dissolution data were also fitted to the well-known exponential equation.

$Mt/M = kt^n$ (4)

Mt/M is the fraction of drug release at time't', and 'k' is the kinetic constant; 'n' is th e release exponent (indicating release mechanism). Irrespective of the excipient type and levels all the drug formulation followed first order kinetics. The *in vitro* release profiles tadalafil formulations containing crospovidone could be best expressed by Higuchi's equation, as the plots showed highest linearity as evident from Table 2 with figures 3 – 8. Diffusion, may therefore, be the mechanism for the drug release from these batches. To confirm the diffusion, the data were fitted in to Peppas equation. The formulation showed a good linearity (r^2:0.907 to 0.988) with slope (n) values ranging from 0.289 to 0.843 for tadalafil indicating that diffusion is the dominant mechanism of drug release with these formulations. When plotted according to Peppas equation, formulation F6 for tadalafil showed good linearity (r^2=0.988), with a slope (n) value of 0.364 respectively. This probably indicates that the drug release of tadalafil is by Non-Fickian diffusion, when the tablet enters an *in vitro* dissolution medium, drug particles initially pass into solution from the surface (immediate release). The *in vitro* drug release profiles were plotted according to zero order, first order, Higuchi and Peppas equations to understand the mechanism of drug release and to compare the differences in the release profile of various batches of tadalafil tablets were given in Table 2 with figures 3 – 7.

Optimization Taguchi plot

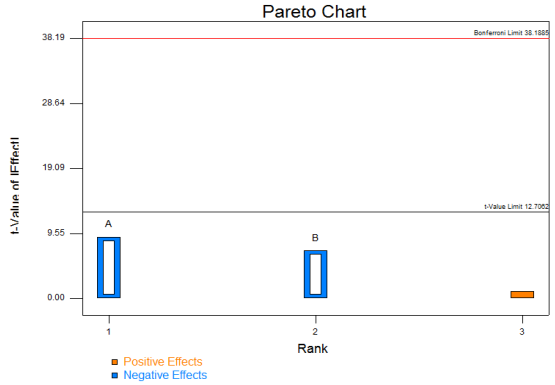

Fig. 8: Taguchi plot for the Disintegration Time.

Except, the amount of MCC, all other process parameters significantly influenced the disintegration time (Figure 8). In the figure, orange colour indicates the parameter has positive effect and blue colour column indicates the negative effect on the particle size uniformity. The white column inside the orange columns and the blue colour indicates that the parameters have significant effect on the disintegration time.

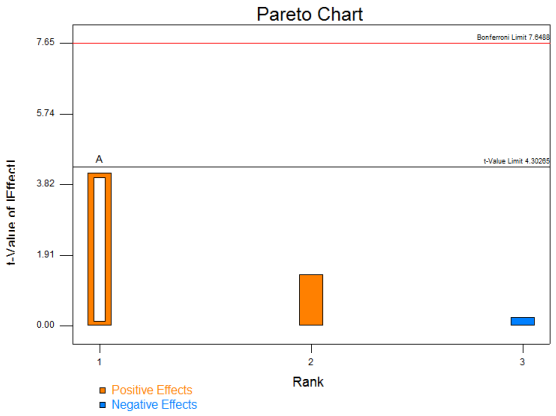

Fig. 9. Taguchi plot for the Drug Release.

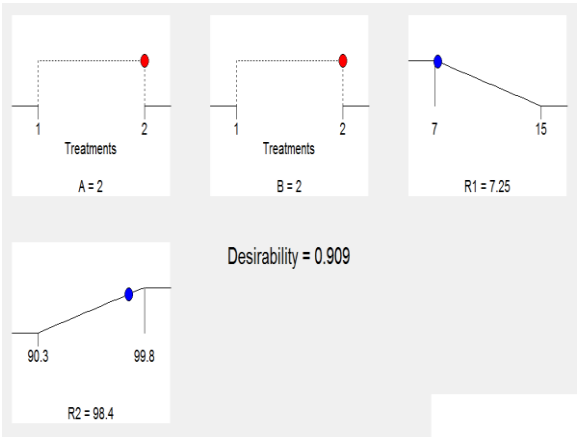

Fig. 10: Fabrication of tablets was displayed in RAMPS.

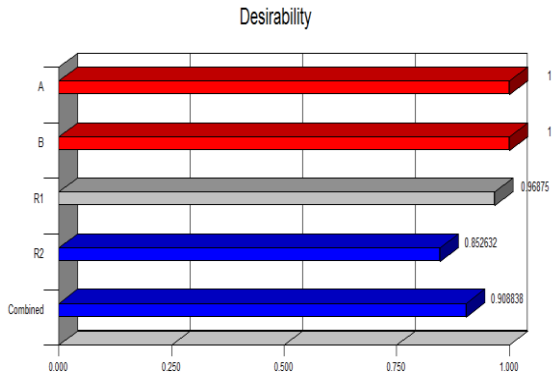

Fig. 11: Desirability of tablets.

The process parameters amount of spray dried lactose significantly influenced the drug release (Figure 9). In the figure, orange colour indicates the parameter has positive effect and blue colour column indicates the negative effect on the particle size uniformity. The white column inside the orange columns and the blue colour indicates that the parameters have significant effect on the drug release. The optimized formula (with desirability: 0.909) for the fabrication of tablets was displayed in RAMPS format ARA (Figure 10- 11).

CONCLUSION

Finally the *in vitro* release of Tadalafil from the prepared FDTs was studied using pH 1.2 as a medium, in which formulation F12 containing Tadalafil-poloxamer ratio (1:3), Kyron as super disintegrating agent shown fastest drug release 99.27±2.78 within 30 minutes. These results were indicating that the time required for drug to release from tablet was decreased, with increasing the concentration of drug to poloxamer by using crospovidone and croscarmellose sodium as superdisintegrants. However, time required for drug release was increased with higher concentration of crospovidone and croscarmellose sodium, because it acts as both superdisintegrant and dissolution enhancer. The *in vitro* drug release profiles, according to zero order, first order, Higuchi and Peppas equations to understand the mechanism of drug release and to compare the differences in the release profile of various batches of tadalafil tablets complied with kinetics and drug release parameter.

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