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Design and Evaluation of Tacrolimus by Using Liquisolid Technology

Chitta.Venkateswararao[1*], J.Venkata Suresh[1], J. Praveen Kumar[1], G.Nagarjuna Reddy[1]

Department of Pharmaceutics, K.L.R.Pharmacy College, Palvoncha, Telangana-507115

ABSTRACT

Liquisolid technique is a new approach for delivery of drugs through oral cavity. This technique is suitable for poorly or water insoluble drugs and also for immediate or sustained release formulations. The technique is based upon the admixture of drug loaded solutions or liquid drug with appropriate carrier and coating materials to convert into acceptably flowing and compressible powder. The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities. Indirectly its leads to enhancement of bioavailibity. Liquisolid tablet of drug Tacrolimus were prepared by using PG, PEG 200, PEG 400, glycerin, Tween 80 and Span 80, as non volatile liquid vehicle, respectively. Tacrolimus is an immunosuppressive drug, which have poor water solubility and low bioavailability, so it is suitable for liquisolid technique. Also Tacrolimus is having daily dose 5-10 mg once a daily. FTIR and DSC studies reveal that there was no possible interaction between drug and tablet excipients. All the formulation was evaluated for disintegration time, hardness and friability time, in-vitro dissolution study.

Keywords: Tacrolimus, Evaluation, Designed, Direct compression, Liquisolid technology.

*Corresponding Author Email: chitta_2013@rediffmail.com

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INTRODUCTION

Liquisolid technique is a new approach for delivery of drugs through oral route. This technique is suitable for poorly or water insoluble drugs and also for immediate or sustained release formulations. The drug is dissolved or dispersed in suitable non-volatile solvent and this liquid medication is converted to free flow powder by using carrier and coating material. To this suitable excipients were added and tableting by direct compression[1]. This is the new technology to improve the solubility of those drugs whose water solubility is poor[2]. During the past few years many techniques have been developed such as drug micronization, solid dispersions, coprecipitation, lyophilization, and microencapsulation, use of prodrug, drug derivetization processes and inclusion of drug solutions into soft gelatin capsules to improve the solubility and bioavailability. Solid dispersion (SD) technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers. Formulation of liquisolid compact (LS) is a novel "Powder Solution Technology" which makes use of liquid medications admixed with suitable carriers and coating materials and formulated into a moderately flowing, dry looking, non adherent and compressible powder forms have increased the drug dissolution rate profiles[3]. The liquisolid technology may also be used to prolong dissolution rate[4-5]. Sustained release oral dosage forms are beneficial with regard to patient compliance because of the reduced dosing frequency. Ideally, a sustained release dosage form leads to therapeutic plasma levels, which are maintained throughout the dosing interval. It has been shown that with hydrophobic carriers such as Eudragit® RL and RS instead of hydrophilic carriers, sustained release systems may be obtained[6]. Tacrolimus is an immunosuppressive drug whose main use is after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It is also used in a topical preparation in the treatment of severe atopic dermatitis, severe refractory verities after bone marrow transplants, and the skin condition vitiligo[7]. The aim of the present study was to investigate the use of liquisolid technique in improving solubility and dissolution profile of Tacrolimus, a poorly soluble drug in the form of a liquisolid compact. New mathematical model is applied to calculate the required amounts of powder excipients (carrier and coating materials) for the formulation of liquisolid systems. 3^2 full factorial design is applied to study the effect of drug: excipient ratio (X1) and drug concentration in liquid medication (X2) on angle of repose, disintegration and dissolution of liquisolid compact of Tacrolimus.

MATERIALS AND METHOD

Materials

Tacrolimus was obtained as gift sample from Bio Chemical & Synthetic Product Ltd, Hyderabad India. PG, PEG 200, PEG 400, glycerin, Tween 80 and Span 80, were purchase from Central drug house, New Delhi. The reagents and chemicals which are used in the formulation are analytical grade.

Method of preparation of liquisolid system

The desired quantity of the previously weighed solid Tacrolimus was dissolved in liquid vehicle (Tween 80). The solution was then sonicated for 15 min until a homogeneous drug solution was obtained. Next, the calculated weights (W) of the resulting liquid medications (equivalent to 10 mg drug) were incorporated into the calculated quantities of the carrier Avicel pH 200 and mixed thoroughly. The resulting wet mixture was then blended with the calculated amount of the coating material Aerosil 200 using a standard mixing process to form simple admixture. Two factors were varied, concentration of the drug in liquid vehicle (Tween 80) and carrier: coating ratios. Different liquid load factors (Lf) ranging from 0.280 to 0.300 were employed. Finally 5% w/w of polyplasone XL-10 was mixed with the above mixture for 10 min. The final blend of liquisolid powder system was compressed into tablets of desired weight of 10 mg strength each by using 9 station tablet compression machine (Rimek Mini Press II-DL Karnavati), flat faced punch and die size of 12 mm were used. Directly compressed conventional tablets (CND) which is used for comparisons with liquisolid compacts is prepared by directly compressing powder mixture of Tacrolimus with Avicel PH 200, Aerosil 200,and polyplasdone XL-10.

Application of the 3^2 factorial designs for designing of Tacrolimus liquisolid system

Full factorial design was employed for the preparation of the liquisolid compacts. Two independent factors are studied, each at three levels, and experimental trials are performed on all 9 possible combinations. Excipients ratio (carrier: coating material, R) and percent drug concentration in liquid medication were selected as independent variables. The angle of repose, disintegration time, percentage cumulative drug release at 30 min was selected as dependent variables.

Application of the mathematical model for designing of Tacrolimus liquisolid system

To calculate the required ingredient quantities, the flow able liquid-retention potentials (F-values) of powder excipients were used. Flow able liquid-retention potential for Avicel pH 200 and Aerosil 200 was 0.16 and 3.33 respectively.

Characterization of liquisolid formulations

Flow properties of the liquisolid system

The flow properties of the liquisolid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was measured by the fixed funnel and free standing cone method. The bulk density and tap densities were determined for the calculation of Hausner's ratio and Carr's Index.

Evaluation of Tacrolimus liquisolid tablets

The hardness of the liquisolid compacts was evaluated by using Monsanto hardness tester. Friability test was performed by using Roche friabilator. Weight variation test was performed was performed as per Indian Pharmacopoeia (IP) by weighing 20 tablets individually on electronic balance, calculating the average weight, and comparing the individual tablets weights to the average. Disintegration test of all formulation was carried out in distilled water by using United State Pharmacopoeia (USP) disintegrating test apparatus by following standard procedure.

Drug content uniformity

Tablets were crushed and powder transferred to 100 ml volumetric flask containing 40 ml of methanol. The flask was shaken to dissolve the drug and adjusted to the volume with methanol to obtain stock solution. Further suitable dilutions were done. The absorbance was recorded at λmax of 210 nm on UV spectrophotometer.

In vitro drug release

The dissolution rates of all formulations were measured in dissolution test apparatus by tablet dissolution apparatus USP Type II. Dissolution studies were carried out using 900 ml of phosphate buffer of pH 7.4 with 0.02% tween 20, as dissolution media, at 50 rpm and at temperature of 37± 0.5 °C. Appropriate aliquots were withdrawn at suitable time interval (5, 10, 15, 20, 25, 30 40, 50, 60 min) and filtered through Whatman filter paper and diluted as per need with Phosphate buffer of pH 7.4. Sink conditions were maintained throughout the study. The samples were then analyzed at λmax of 210 nm by UV/visible spectrophotometer. The study was carried out in triplicate.

Stability studies

Selected formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for stability testing.

1. 25^0C/60% RH analyzed every month for period of three months.
2. 30^0C/75% RH analyzed every month for period of three months.
3. 40^0C/75% RH analyzed every month for period of three months.

RESULTS AND DISCUSSION

Calibration curve

The method obeyed Beer's law in the concentration range of 1 -10 µg/ml. Low RSD (< 0.35) values ensured reproducibility of the method.

Evaluation of flow properties

Angle of repose were found to be in the range of 27-39 indicating acceptable flow properties and this was further supported by lower compressibility index values shown in Table.2. Surface response graph of the angle repose in Figure. 2 and 3 showing that, as drug: excipient ratio (R) liquid and drug concentration in liquid medication increases flow properties is improved. Formulation F7, F8, F9 has better flow property as compared to other formulation. The percent compressibility for all formulations lies within the range of 14.32±3.20 to 20.89±0.897. Hausner's ratio was found to be in a range of 1.17±0.092 to 1.25±0.016.

Table 1: Calibration plot of Tacrolimus Liquisolid Tablets

Concentration (µg/ml)	Absorbance	
	Mean	RSD
0	0	0
1	0.061	0.26
2	0.126	0.35
4	0.229	0.29
6	0.317	0.33
8	0.399	0.12
10	0.495	0.18

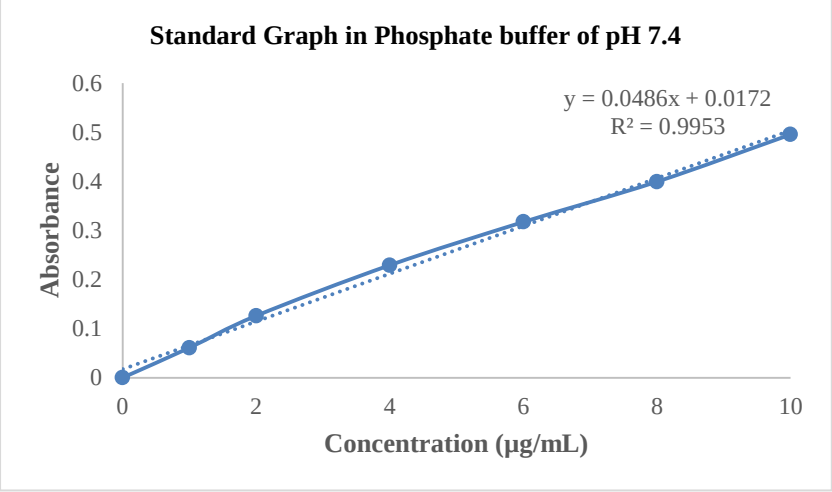

Figure 1: Calibration plot of Tacrolimus liquisolid tablets

Evaluation of Tacrolimus liquisolid tablets

Tablet dimensions

Thickness of liquisolid compacts ranged from 2.04±0.09 to 6.65±0.01 mm and diameter of all the liquisolid compacts was found to be in the range of 12.34 ± 0.01 to12.37 ± 0.01 mm.

Hardness

Hardness was found to be in the range of 3.0± 0.38 to 4.6 ± 0.45 kg/cm^2. It is seen that as the amount of Avicel goes on increasing, hardness also increases. With decrease in R values, hardness was decreased. This low hardness could be attributed to the less amount of added Avicel and poor compressibility of Aerosil. The hydrogen bonds between hydrogen groups on adjacent cellulose molecules in Avicel PH 200 may account almost exclusively for the strength and cohesiveness of compacts.

Table 2: Rheological Properties of Granules

Formulation Code	Angle pf Repose	Carr's Index (%)	Hausner's Ratio
F1	38.23± 0.005	20.89±0.897	1.25±0.016
F2	32.40±0.002	19.56±3.56	1.24±0.026
F3	29.36±0.026	19.27±3.84	1.23±0.037
F4	37.8±0.018	17.65±2.65	1.22±0.045
F5	30.79±0.016	16.52±2.10	1.21±0.052
F6	30.00±0.023	16.00±1.98	1.20±0.060
F7	29.85±0.029	15.85±2.89	1.19±0.075
F8	28.46±0.030	14.96±2.56	1.18±0.086
F9	27.86±0.015	14.32±3.20	1.17±0.092

Weight variation test

Weight variation test were performed as per IP. All the tablets were within the range of Pharmacopoeia specifications as shown in Table.3.

Friability

All the liquisolid compacts had acceptable friability as none of the tested formulation had percentage loss in tablet's weights that exceed 1% as shown in Table.3.

Disintegration time

The disintegration test revealed that the all the liquisolid tablet were disintegrated within 15 min as shown in Table.3.

Table 3: Comparative data for Evaluation of Various Properties of Tacrolimus Tablets

Formulation Code	Hardness (Kg/cm2)	Weight Variation (mg)	Friability (%)	Disintegration Time (Sec)	% Drug Content	% Drug release in 30 min
F1	4.5±0.45	473.68±0.45	0.64	102.64	100.86	92.46
F2	3.8±0.56	317.36±0.85	0.52	152.56	99.79	82.45
F3	3.0±0.38	236.84±0.64	0.38	189.49	100.2	69.74
F4	4.6±0.45	480.33±0.96	0.54	125.64	99.74	93.48

F5	3.7±0.56	321.82±0.86	0.62	176.59	99.69	85.26
F6	3.2±0.38	240.16±0.85	0.64	195.64	100.73	75.64
F7	4.6±0.48	490.6±1.01	0.43	139.24	100.26	100.28
F8	3.9±0.62	328.7±0.98	0.52	189.59	100.94	87.24
F9	3.2±0.45	245.3±0.94	0.54	203.79	100.09	84.69
Control	3.1±0.34	251.5±0.87	0.22	149.87	99.48	38.94

FTIR Interference evaluation

The FTIR spectra of pure drug and formulation are shown in Figure.4. It is clear that the characteristic peaks at 3323 cm-1 (asymmetry N-H stretching), 3249 cm-1 (symmetry N-H stretching), 2937 cm-1, 2856 cm-1 (aliphatic C-H stretching), 1689 cm-1 (mono amide C-O stretching), 1649 cm-1 (diamide C-O stretching), 1528 cm-1, 1444 cm-1 (C-C and C-N stretching),1331 cm-1 (asymmetry S-O stretching),1158 cm-1 (symmetry S-O stretching), 1032 cm-1, 899 cm-1 (S-O-C stretching) are seen in both pure Tacrolimus and its formulation without any change in their position, indicating no chemical interaction between Tacrolimus and excipients. FT-IR spectra indicated no interaction between Tacrolimus and the formulations.

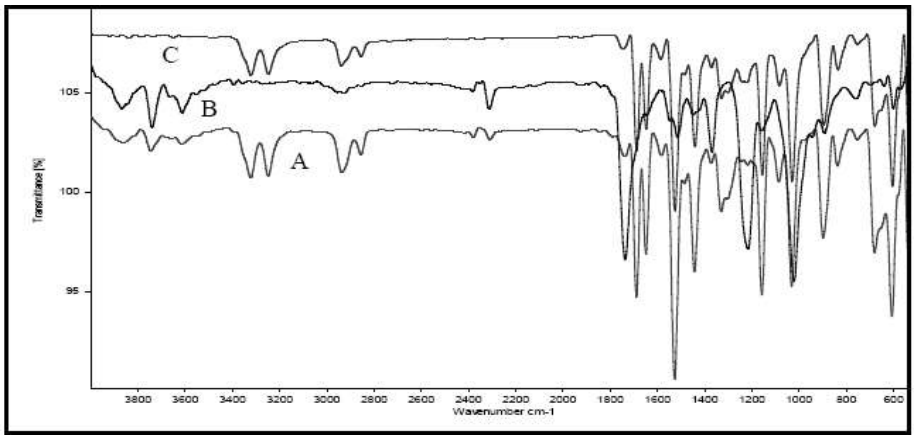

Figure 4 FTIR of Tacrolimus liquisolid tablets

DSC evaluation

DSC thermogram of the liquisolid tablets was compared with the DSC theromogram of pure drug sample. The pure Tacrolimus displayed a single sharp endothermic peak at 218.760C corresponding to the melting point of the drug, and a similar peak was also observed in the formulation shown in Figure.5. The DSC thermogram, thus, confirms that there is no interaction between the polymer starch acetate and drug Tacrolimus. DSC spectra indicated no interaction between Tacrolimus and the formulations.

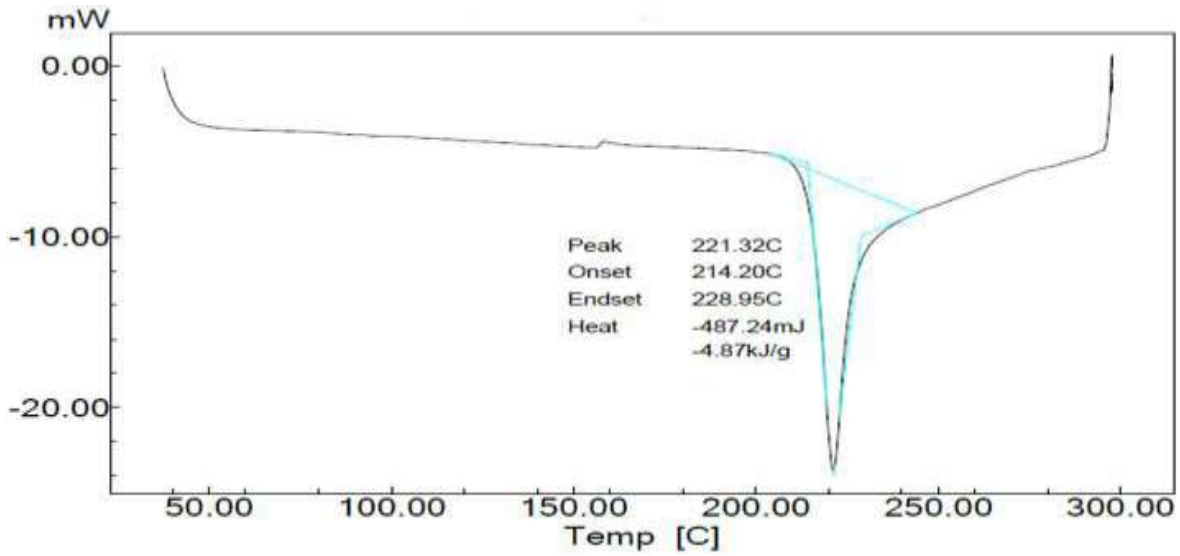

Figure 5 DSC of Tacrolimus liquisolid tablets

In-vitro release evaluation

The dissolution profiles of Tacrolimus from liquisolid tablets (F1 to F9) produced higher drug dissolution rate in comparison with the conventional tablets in Phosphate buffer of pH 7.4 with 0.02% tween 20. It was apparent that F7 formulation has the highest dissolution rate. The percentage of Tacrolimus dissolved from F7 reached 100.28% after only 30 min, while the control had maximum Tacrolimus content (38.94%) dissolved after 30 min. While control had a maximum drug released of 56% in 60 min. The enhanced dissolution rates of liquisolid compacts compared to control may be attributed to the fact that, the drug is already in solution in Tween 80, while at the same time, it is carried by the powder particles. From the surface response graph it is clear that drug release is decreased with an increase in concentration of drug in liquid medication. The drug release properties of liquisolid compacts were improved with increasing powder excipients ratio (R). Therefore, the liquisolid tablets with high R values and lower drug concentration in liquid medication, F7 showed maximal drug release at 30 min and 100.28% while that of F3 had minimum of 69.74% drug release at 30 min.

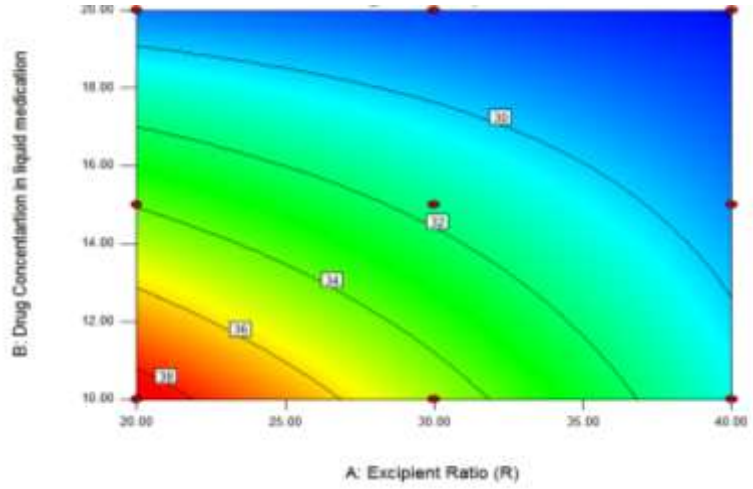

Figure 2: Contour plot of Tacrolimus liquisolid tablets

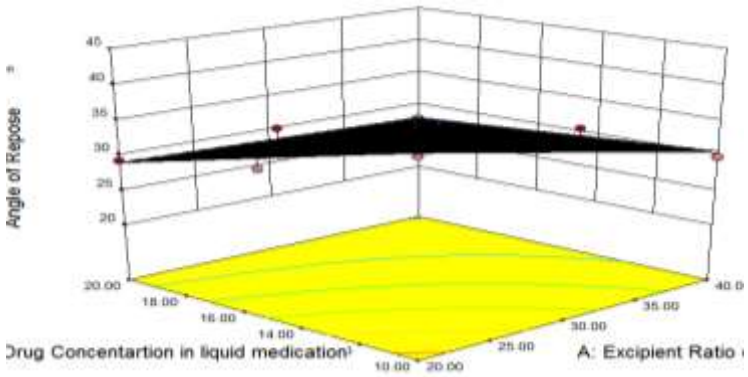

Figure 3 Surface 3D graph Tacrolimus liquisolid tablets

Stability evaluation

There were no significant changes in physical and chemical properties of tablets of formulation F7 after 3 months. Parameters quantified at various time intervals were shown Table.4.

Table 4: Stability Studies of Optimised Formulation F7

Formulation code	Parameters	Initial	1st Month	3rd Month	Limits as per specifications
F7	25˚C/60%RH % Release	97.11	96.87	96.65	Not less than 85%
F7	30˚C/75%RH % Release	97.05	96.89	96.88	Not less than 85%
F7	40˚C/75%RH % Release	97.11	96.88	96.63	Not less than 85%
F7	25˚C/60%RH Assay value	98.16	98.10	98.12	Not less than 90% Not more than 110%
F7	30˚C/75%RH Assay value	98.12	98.11	98.10	Not less than 90% Not more than 110%
F7	40˚C/75%RH Assay value	98.16	98.10	98.10	Not less than 90% Not more than 110%

DISCUSSION:

Liquisolid tablet is the technique in which the drug is mixed with non-volatile solvent and which is

again mixed with carrier and coating material which have specified ratio and finally added super disintegrants and glidants. Tacrolimus tablet where prepared by liquisolid system. In literature the liquisolid tablet of Tacrolimus no work on this technique for solubility enhancement hence the study is selected. Other techniques for solubility enhancement are given on this drug such as solid dispersion, nanoemulsion, In this technique authentic mechanism of increasing in solubility is the wetting of drug particle and increase in surface area of the drug due to that the solubility of drug get increased. The research show that the solubility of Tacrolimus is very less in water and hence the various non-volatile solvents having more solubility than the water hence among polyethylene glycol, propylene glycol, tween-80, glycerin shows more solubility of Tacrolimus. Hence polyethylene glycols are selected for the preparation of liquisolid tablets. The microcrystalline cellulose (Avicel pH-200) and aerosil-200 was selected as carrier and coating material. The FT-IR and DSC studies show no interaction between drug and excipients. The finally compressed into the tablets using tableting machine by alternatively checking hardness of the tablets. The evaluation of the liquisolid tablets was done by two parts such as pre-compression study and post-compression study. In pre-compression study the all parameters like flow properties- bulk density, tap density, angle of repose, Hausner's ratio and Carr's index was performed and shows the significant results. In post compression evaluation the diameter, thickness, hardness, weight variation, disintegration time, friability was done. The in-vitro evaluation of the Tacrolimus liquisolid tablets compared with all batches the batch having more non-volatile solvent shows fast release of the drug from the tablets such as batch F7 shows fast release of drug than other batches. The batch F7 which is compared with plain drug and conventional tablets. The liquisolid tablets show significant release than that plain drug and conventional tablet. Hence the liquisolid tablet is the promising tool for enhancement of solubility of water insoluble drug.

CONCLUSION

The liquisolid tablets technique can be an auspicious standby for the formulations of water-insoluble drugs, such as Tacrolimus into fast release tablets. The higher dissolution rates of formulation F7 displayed by liquisolid tables may also implicit enhanced oral bioavailability due to the increased wetting properties and the surface of drug available for dissolution. It can also be concluded that from this study, the investigated liquisolid compacts of Tacrolimus with increasing the amount of carrier to coating ratio along with super disintegrating agent also resulted in higher dissolution rate, which are directly proportional to the amount of drug released.

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