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Application of Mathematical Models in Drug Release Kinetics of Cyanocobalamine Fast Dissolving Sublingual Film

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The aim of present work is to determine and analyse the kinetics of drug release from the fast dissolving sublingual by employing various mathematical models. A study was done with Cyanocobalamine fast dissolving sublingual films, 1.5 mg/film by employing solvent casting technique using dehydrated banana starch and Gelatin. The in-vitro drug release profile was carried out in pH 6.8 phosphate buffer (900 mL) using USP dissolution apparatus I (Basket) at 50 rpm for 20 mins. The drug release data was obtained, quantitatively correlated and interpreted with various mathematical models viz. Zero order model, first order model, Higuchi model, Hixson-Crowell model and Korsmeyer-Peppas model and evaluated to understand the kinetics of drug release. The criterion for the most suitable model was based on the high degree of coefficient of correlation of drug release profile of Cyanocobalamine fast dissolving sublingual films.

Keywords: Dissolution; diffusion; coefficient of correlation; kinetics of drug release.

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1. INTRODUCTION

At the time solid particles come in contact with the GI tract, a saturated layer of drug solution is generated rapidly on the surface of particles in the liquid closely surrounding them (named the diffusion layer). The drug molecules at that time diffuse through the GI content to the lipoidal membrane where diffusion through the gastro intestinal membrane and absorption into the circulation takes place.

There are two likely situations for the drug dissolution.

1. Absorption from solution proceeds subsequent the quick dissolution of solid particles. In this situation rate of absorption is controlled by rate of diffusion into the GI fluid.
2. Absorption from solution proceeds subsequent the sluggish dissolution of solid particles. In this case rate of absorption is controlled by rate of dissolution into the GI fluid.

Therefore, dissolution is a process in which a solid material solubilises in a particular solvent i.e., mass transfer from solid surface to the liquid phase [1].

2. THEORIES OF DRUG DISSOLUTION

Numerous theories have been suggested to elucidate drug dissolution. Some of the significant ones are:

- Diffusion layer model/ film theory.
- Danckwert model/ penetration or surface renewal theory.
- Interfacial barrier model/ double barrier or limited salvation theory.

2.1 Diffusion Layer Model/ Film Theory

This model ponders that a layer of liquid, H cm thickness, close to the solid surface remains stationary as the majority liquid passes over the surface with a specific speed (Fig. 1). The contact at the solid/liquid boundary is considered to be freely formation of a saturated solution, C_S, of the solid in the stationary liquid layer. The rate of dissolution is carried out by the diffusion of the solid molecules from the stationary liquid film to the bulk liquid according to Fick's first law:

$$J = - D_f \, dc/dx$$

Where J is the quantity of substance passing perpendicularly through a unit surface area per time, D_f is the diffusion coefficient and dc/dx, is the concentration gradient. After a time t, the concentration among the limit of the stationary liquid layer and the bulk liquid becomes C_t. Once the solid molecules goes into the bulk liquid, it is presumed that there is speedy mixing and the concentration gradient vanishes. This theory describes that a constant rate of dissolution can be attained if the concentration gradient is continuously constant i.e., $C_S - C_t$ is constant as $C_S >> C_t$ (as in "sink" conditions which generally mean $C_S > 10\ C_t$).

2.2 Danckwert Model/ Penetration or Surface Renewal Theory

This model ponders that there is creation of macroscopic packets of solvent that confers at the solid /liquid boundary in a diffusion method (Fig. 2). Therefore at the boundary, the packet is able to absorb solute rendering to the laws of diffusion which is to be substituted by a new packet of solvent. This surface regeneration process is associated to the rate of transfer of solute and lastly to the rate of dissolution. However the diffusion layer model is the utmost commonly used, various modifications have been suggested. The existing interpretations of the diffusion layer model are created on the alleged actual diffusion boundary layer, the structure of which is deeply reliant on the hydrodynamic situations. Aguiar et al. signified a theory which holds that dissolution happens only when the drug is in small particles. Wagner changed above theory and displayed that dissolution happens from both the unbroken tablet and the aggregates and/or granules formed after disintegration.

2.3 Interfacial Barrier Model/ Double Barrier or Limited Salvation Theory

In this model, it can be deliberated that the interaction at the solid/liquid boundary is not natural due to a high activation free energy barrier which is to be encircled before the solid can dissolve (Fig. 3). Thus, the dissolution mechanism is almost same as in diffusion layer model, with the concentration at the limit of the stationary layer of liquid becoming C_t after time t. The rate of diffusion in the stationary layer is comparatively fast in association with the existence of the energy barrier, therefore it becomes rate limiting in the dissolution process.

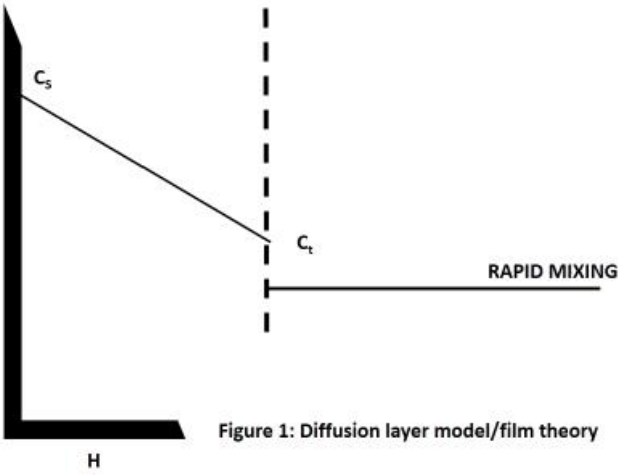

Figure 1: Diffusion layer model/film theory

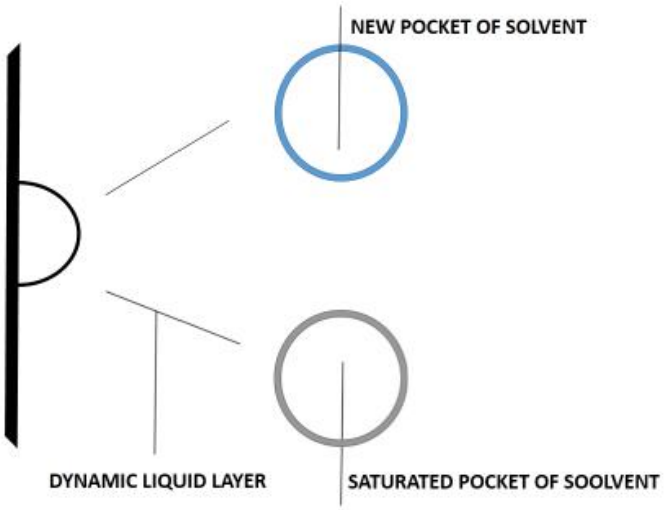

Figure 2: Danckwert model/penetration or Surface renewal theory

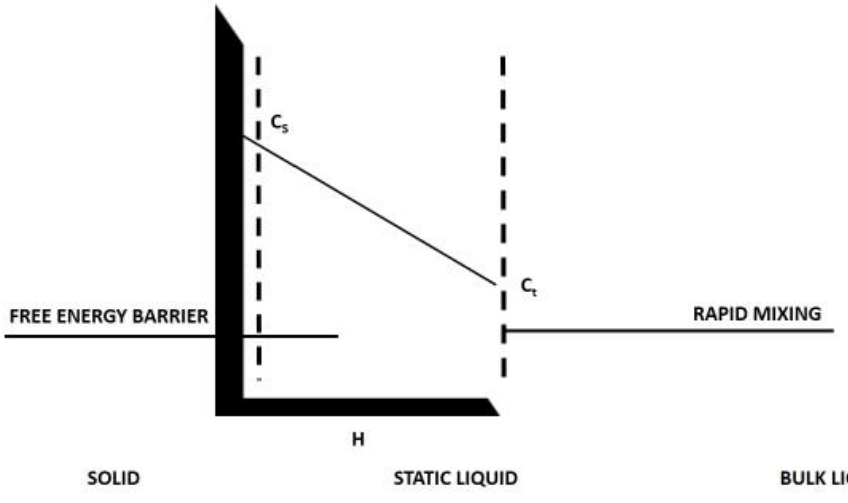

Figure 3: Interfacial barrier model/double barrier or limited salvation theory

3. BASICS OF KINETICS OF DRUG RELEASE

3.1 Laws in the Kinetics of Drug Release

3.1.1 Noyes-Whitney law

Noyes-Whitney created the basic principle of evaluation of drug release that explains as

$$d_C/d_t=K (C_s - C_t)$$

Where

d_C/d_t is dissolution rate of drug,

K is dissolution rate constant,

C_s is the concentration of drug in the stagnant layer (also called as the saturation or maximum drug solubility),

C_t is the concentration of the drug in the bulk of the solution at time t.

3.1.2 Fick's law of diffusion

As per this law drug molecules diffuse from a region of higher concentration to one of lower concentration up until balance is attained and that the rate of diffusion is directly proportional to concentration gradient across the membrane.

This can be expressed mathematically as

$$dQ/dt=DAK_{m/w}(C_{GIT}- C)/h$$

Where

d_Q/d_t is rate of drug diffusion, amount per time (rate of appreance of drug in blood),

D is the diffusion coefficient. Its dimension is area per unit time, so typical units for expressing it would be m^2/s (area/time),

A is the surface area for absorbing membrane for drug diffusion (area),

$K_{m/w}$ Partition coefficient of drug between lipoidal membrane and aqueous GI fluid (no unit),

C_{GIT}- C is the difference in the concentration of drug in the GI fluid and the plasma called concentration gradient (amount per volume),

h is the thickness of the membrane (length) [2].

4. FORMULATION OF FAST DISSOLVING SUBLINGUAL FILM OF CYANOCOBALAMINE

The sublingual route has been an attractive option for the administration of many drugs directly into systemic circulation for many researchers. Factors like rich vascularization and good permeability or buccal mucosa make this route more attractive in comparison to oral and parenteral routes. Absorption of many drugs delivered orally is adversely affected by hepatic metabolism. Also, it has been observed that the enzymatic degradation and the destructive effect of acidic environment in the gastric region lead to the low oral bioavailability. The use of fast disintegrating polymers in the formulation of buccal mucosal dosage forms decreases disintegration time of dosage at the site of application. In comparison to parenteral drug delivery system, sublingual drug delivery system can administer the drug into systemic circulation in a completely pain-free manner. Other advantages include self-medication and termination of therapy in case of adverse effects.

Cyanocobalamin, also known as cobalamin, is a water-soluble vitamin that is active in every cell of the human body's metabolism. This vitamin is one of eight B vitamins. In DNA synthesis and in the metabolism of both fatty acids and amino acids, it is a cofactor. It is especially important for the proper functioning of the nervous system through its role in myelin synthesis and the maturation of red blood cell production in the bone marrow. The highest and most structurally complex vitamin is Cyanocobalamin. There are four nearly similar molecular classes (vitamins) of this vitamin: cyanocobalamin, hydroxocobalamin, adenosylcobalamin, and methylcobalamin [3].

In the present study, an attempt was made to design Carbidopa and Levodopa ER Tablet and its release profile was interpreted with various mathematical models [4].

- Zero order model
- First order model
- Higuchi model
- Korsmeyer -Peppas model
- Hixson-Crowell model

4.1 Materials and Methods

Cyanocobalamin was received as gift samples from Sun pharmaceuticals Ltd., Halol, India.

Gelatin Dehydrated banana starch and mannitol was obtained from Loba Chemie, Mumbai, India. PEG 400 was obtained from Qualikems Fine Chem, Vadodara, India.

4.2 Method of Preparation of Fast Dissolving Sublingual Films

Fast dissolving sublingual film of Cyanocobalamine was prepared by using solvent casting method. All water soluble ingredients are dissolved in the ascending order of their quantity into distilled water. To this the required quantity of PEG 400 was added and the solution was mixed well. The solution was sonicated for 30 min to remove any entrapped air. The solution was then castes in a petri plate and kept in over at 60˚C for 24 hr. The dried film was removed and cut into square shape pieces with 2 cm^2 area.

4.3 *In-vitro* Dissolution

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 phosphate buffer maintained at 37±0.50 ˚C at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer. Cyanocobalamine in the samples was then determined spectrophotometrically at λmax of 361 nm. The results were expressed as mean of three determinations.

5. APPLICATION OF DRUG RELEASE DATA ON MATHEMATICAL MODELS

Numerous mathematical equations which usually describe the dissolution profile. Once a suitable meaning has been selected, the assessment of dissolution profile can be done and therefore the drug release profile can be linked with drug release kinetic models. Numerous mathematical models are used to comprehend drug release kinetics.

5.1 Zero Order Model

As per the principles of pharmacokinetics, drug release from the dosage form can be represented by the equation:

$$C_0 - C_t = K_0 t$$

$$C_t = C_0 + K_0 t$$

C_t is the amount of drug released at time t,
C_0 is the initial concentration of drug at time t=0,
K_0 is the zero-order rate constant.

Therefore, zero order kinetics describes the process of continuous drug release from a drug delivery system and drug level in the blood remains constant throughout the delivery.

Henceforth to learn the drug release kinetics data attained from *in-vitro* dissolution study is plotted against time i.e., cumulative drug release *vs.* time.

Therefore the slope of the above plot provides the zero-order rate constant and the correlation coefficient of the above plot will provide the information whether the drug release follows zero order kinetics or not.

Therefore, this model was used in the release profile of Cyanocobalamine fast dissolving sublingual film, 1.5 mg/film (Table 1) and evaluation was done in the graphical presentation (Fig. 1) [5].

The graphical depiction of cumulative % of drug release against time describes that drug release of Cyanocobalamine from the polymeric film does not follow seamlessly the principle of zero order release kinetics, yet it is slightly approaching, r^2=0.985.

5.2 First Order Model

The release of drug which follows first order kinetics can be signified by the equation:

$$DC/dt = -K_1 C$$

K_1 is the first order rate constant, expressed in $time^{-1}$ or per hour.

Therefore it can be well-defined that first order process is the one whose rate is directly proportional to the concentration of drug go through reaction i.e., greater the concentration faster the reaction. Henceforth, it follows linear kinetics.

After rearranging and integrating the equation,

$$\log C = \log C_0 - K_1 t/2.303$$

K_1 is the first order rate equation expressed in $time^{-1}$ or per hour,

C_0 is the initial concentration of the drug,

C is the percent of drug remaining at time t.

Therefore to undertand the drug release kinetics data acquired from *in-vitro* dissolution study is plotted against time i.e., log % of drug remaining *vs.* time and the slope of the plot gives the first order rate constant. The correlation coefficient of the above plot will give the evidence whether the drug release follows first order kinetics or not.

5.3 Higuchi Model

The release of a drug from a drug delivery system (DDS) includes both dissolution and diffusion. Numerous mathematical equations models define drug dissolution and/or release from DDS. In the present age of controlled-release oral formulations, 'Higuchi equation' has turned out to be a important kinetic equation in its own right, as showed by using drug dissolution studies that are acknowledged as an significant element in drug delivery development. Today the Higuchi equation is known as one of the extensively used and the most famous controlled-release equation.

The classical basic Higuchi equation is represented by

$$Q = A\sqrt{D\,(2C_O - C_S)C_S t}$$

Where

Q is the cumulative amount of drug released in time t per unit area,

C_O is the initial drug concentration,

C_S is the drug solubility in the matrix and

D is the diffusion coefficient of the drug molecule in the matrix

This relation is valid until total depletion of the drug in the dosage form is achieved.

Tortuisity is defined as the dimensions of radius and branching of the pores and canals in the matrix. After making things easier the above equation, Higuchi equation can be represented in the simplified form

$$Q = K_H \times t^{1/2}$$

Where, K_H is the Higuchi dissolution constant.

It is significant to note that a few assumptions are prepared in this Higuchi model. These assumptions are:

(i) The early drug concentration in the system is much higher than the matrix solubility
(ii) Perfect sink conditions are retained
(iii) The diffusivity of the drug is constant and
(iv) The swelling of the polymer is negligible. The sink conditions are attained by safeguarding the concentration of the released drug in the release medium never reaches more than 10 per cent of its saturation solubility [6].

The graphical representation of cumulative % of drug release against time represents that drug release of Cyanocobalamine from the polymeric film is perfectly following Higuchi drug release model as the drug release profile is very closest to trend line or regression line, r^2= 0.9636, and there is highest value of coefficient of correlation [7].

5.4 Korsmeyer-peppas Model

Once it has been established that the leading mechanism of drug release is diffusion controlled from Higuchi plot then it comes the release of drug follows that type of diffusion [8].

Korsmeyer and Peppas state a simple relationship that defined the drug release from a polymeric system follow which type of dissolution and he represented a equation as:

$$M_t/M_\infty = K_{kp}t^n$$

M_t/M_∞ is a fraction of drug released at time t,

$\log(M_t/M_\infty) = \log K_{kp} + n\log t$

M_t is the amount of drug released in time t,

M_∞ is the amount of drug released after time ∞,

n is the diffusional exponent or drug release exponent,

K_{kp} is the Korsmeyer release rate constant.

To study release kinetics a graph is plotted between log cummulative % drug release $\log(M_t/M_\infty)$ *vs.* log time (log t) [9].

From the above figure (Fig. 5) the slope of the plot was constructed which defined that the release exponent or the diffusion exponent found to be higher than 0.68 which suggests that the drug release from the system follow Non -Fickian transport [10].

Table 1. Composition of Cyanocobalamine fast dissolving films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cyanocobalamine (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Gelatin (%w/w)	10	15	20	10	15	20	10	15	20
Dehydrated banana starch (%w/w)	5	7.5	10	5	7.5	10	5	7.5	10
PEG 400 (%v/w)	2	2	2	4	4	4	6	6	6
Mannitol (%w/w)	2	2	2	2	2	2	2	2	2
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs

Table 2. Comparative in vitro dissolution of formulations in pH 6.8 phosphate buffer

Time	Formulation code								
(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	41.5±0.89	35.5±0.38	27.7±0.70	41.2±0.48	32.3±1.05	26.3±0.84	34.3±1.20	31.9±0.94	25.4±0.84
10	66.2±1.29	59.7±0.59	46.8±0.55	67.7±0.57	52.9±0.22	48.4±1.39	61.5±0.03	52.6±0.55	47.5±1.39
15	87.8±0.99	78.8±0.83	60.6±0.69	88.1±0.62	70.1±0.72	61.1±0.54	78.6±0.46	67.8±0.43	60.2±0.54
20	91.9±0.34	90.7±0.45	79.6±0.48	91.8±0.75	85.3±0.39	80.4±2.03	90.3±0.77	84.5±0.28	81.5±2.03
25	92.1±0.53	92.7±0.74	92.3±0.18	92.3±0.13	93.4±0.57	93.6±0.25	92.9±0.63	92.5±0.49	92.7±0.25

Table 3. Drug release profile of F6 formulation containing 1.5 mg of Cyanocobalamine per fast dissolving sublingual film

Time (min.)	SQRT of Time	Log time	% CDR	Log % CDR	% CD Remaining	Cube root of % CD Remaining
0	0	0	0	0	2	4.641588834
5	2.236067977	0.698970004	26.3	0.69897	1.867467488	4.192655342
10	3.16227766	1	48.4	1	1.712649702	3.72291597
15	3.872983346	1.176091259	61.1	1.176091	1.589949601	3.388310491
20	4.472135955	1.301029996	80.4	1.30103	1.292256071	2.6961995
25	5	1.397940009	93.6	1.39794	0.806179974	1.856635533

Table 4. Results of Different models in terms of r^2, slope and intercept

Model name	F6 formulation containing 1.5 mg of Cyanocobalamine per fast dissolving sublingual film		
	r^2	Slope	Intercept
Zero order model	0.985	3.6743	5.7048
First order model	0.9181	-0.0447	2.1031
Higuchi model	0.9636	18.743	6.9194
Korsmeyer –Peppas model	0.656	-0.6822	2.1785

6. RESULTS AND DISCUSSION

The *in-vitro* drug release profile was applied in various mathematical models and was interpreted in the form of graphical presentation and evaluated by correlation coefficient (r^2) represented in Table 4. The highest degree of correlation coefficient defines the suitable mathematical model that follows drug release kinetics [11]. From the above comparison, it was found that Higuchi square root model showed higher degree of correlation coefficient (r^2) than other models. Therefore, drug release profile of Cyanocobalamine fast dissolving sublingual film (1.5 mg/film) follows diffusion drug release mechanism [12]. Likewise, the model Korsmeyer-Peppas power law equation states the type of diffusion, which was assessed by value, n which is higher than 0.68 which implies that the drug release from the system follow non fickian drug release mechanism [13].

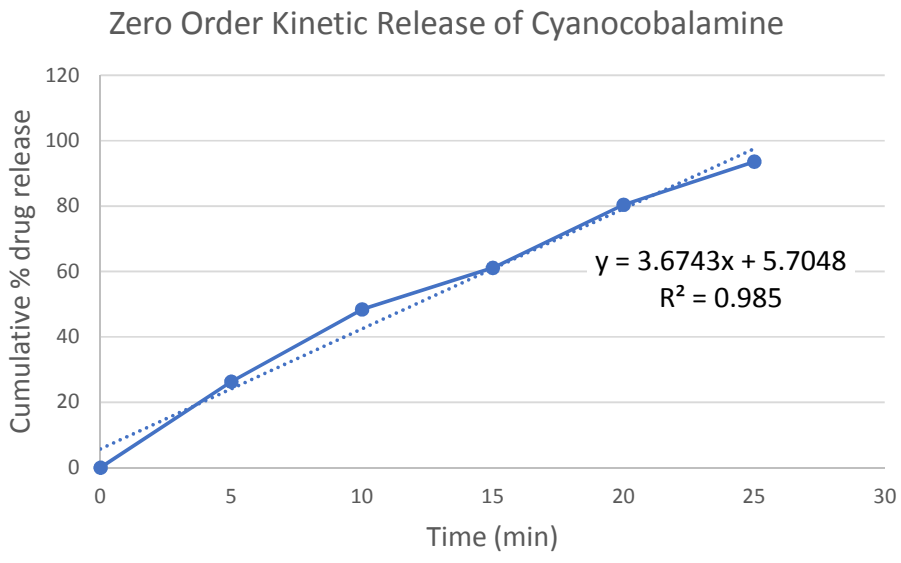

Fig. 4. Zero Order Kinetic Release of Cyanocobalamine

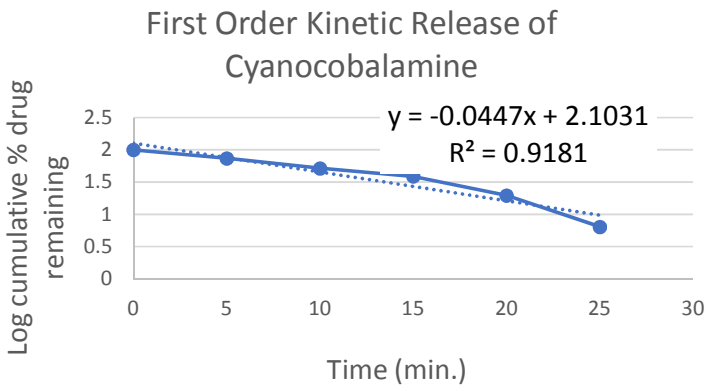

Fig. 5. First Order Kinetic Release of Cyanocobalamine

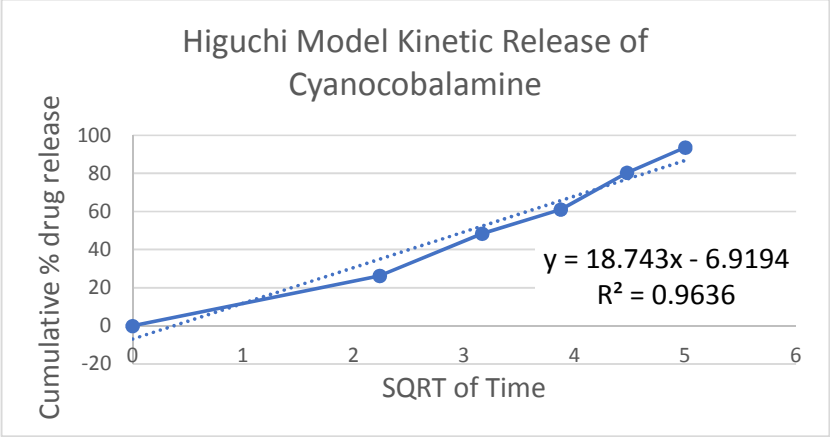

Fig. 6. Higuchi Model Kinetic Release of Cyanocobalamine

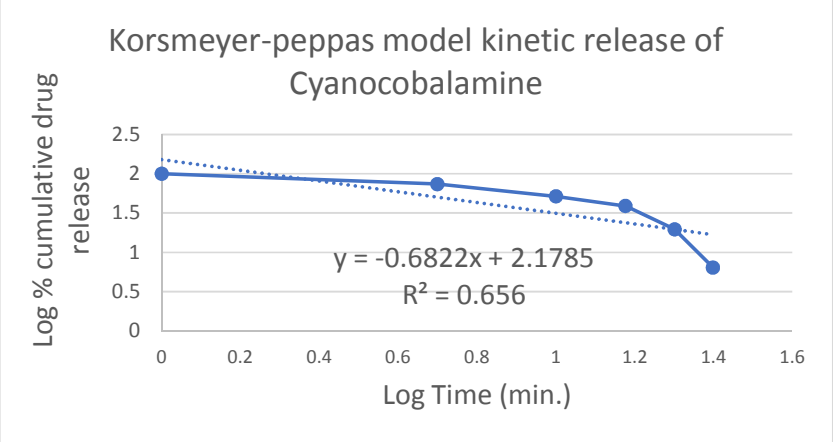

Fig. 7. Korsmeyer-peppas model kinetic release of Cyanocobalamine

7. CONCLUSION

Mathematical models play a vital role in the understanding of mechanism of drug release from a dosage form. It is a significant tool to comprehend the drug release kinetics of a dosage form. The sublingual films of Cyanocobalamin were made in this research

paper showed a satisfactory release profile with the dehydrated banana starch and gelatin. The drug release was found to be best fitted by Higuchi square root model (r^2=0.9636) which implies that release of drug from matrix as a square root of time dependent process and diffusion controlled. Likewise, the model Korsmeyer-Peppas power law equation states the type of diffusion, which was evaluated by value, n (Release exponent) which is higher than 0.68 which implies that the drug release from the system follow non fickian drug release mechanism.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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