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*Original Research Article*

# COMPARISON OF IN VITRO DISSOLUTION PROFILES OF MARKETED DICYCLOMINE HYDROCHLORIDE TABLETS

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## ABSTRACT

In this study, comparison methods for in vitro dissolution profiles of conventional marketed dicyclomine as performed. Dissolution testing was conducted using the USP monograph for Dicyclomine hydrochloride tablet. The comparison of in vitro dissolution profile was based upon model dependent methods and model independent models. The model dependent methods includes kinetic modeling and model independent method includes difference factor, $f_1$ and similarity factor, $f_2$. The $f_1$ factor seems to be easy to apply and interpret; only one value is obtained to describe closeness of the two dissolution profiles. Here dissolution profile follows Higuchi and Hixson – Crowell model while the f1 and f2 value were obtained in the range.

**Key Words:** Dissolution, Dicyclomine Hydrochloride, In vitro release, Difference factor, Similarity factor.

## INTRODUCTION

### Dissolution[1-4]

A drug is expected to be released from solid dosage forms (granules, tablets, capsules, etc) and immediately go into molecular solution. This process is called dissolution.

-It is a critical step for performance of a drug as well as dosage form, because it is a prerequisite for the drug absorption.

-Absorption of drug is possible only when it is present in solution form, wherein the molecules are independent and assume molecular dispersion. Each molecules is absorbed independently through biological membranes.

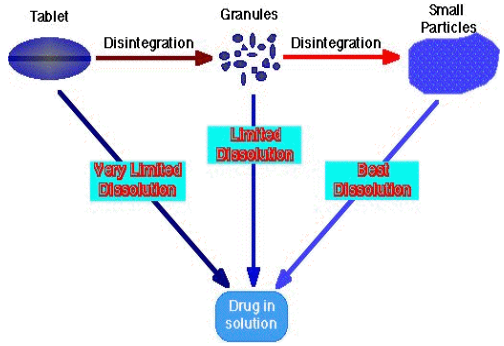



**Fig.1.Different stages depicting the drug absorption from tablet dosage form**

### Factors affecting dissolution[5-8]

A. *Factors relating dissolution apparatus and Dissolution test parameters* (Instrumental factors):-
temp, agitation, speed, dissolution medium & pH

*B. Factors related to drug (physicochemical factors):-*
particle size, shape, surface area, form (amorphous, crystalline) or state of drug (salt), polymorphism

*C. Factors related to dosage form:-*
excipient related factors
(diluent, disintegrant, binder, lubricant, surfactant, coating)
processing related factor (method of granulation, compression force)

### Dissolution test apparatus[9-14]

Dissolution test is specified for it's compliance in the individual monographs of pharmacopoeias, particularly for tablets and capsules. A numbers of apparatus is available to conduct dissolution studies, because no single equipment is adequate for the study of all drugs and dosage forms. Therefore, the objectives of the test defined first.

Depending on the nature of active ingredients and the types of dosage forms, an efficient dissolution method can be developed.

To date, in vitro dissolution tests seems to be the most sensitive and reliable predictors of in vivo performance.

**Table.1.Various official dissolution test apparatus**

| Type | I.P. | USP | B.P. / J.P. | E.P. |
|---|---|---|---|---|
| I | paddle apparatus | basket apparatus | basket apparatus | paddle apparatus |
| II | basket apparatus | paddle apparatus | Paddle apparatus | basket apparatus |
| III | - | Reciprocating cylinder | flow through cell apparatus | flow through cell apparatus |
| IV | - | flow through cell apparatus | - | - |
| V | - | Paddle overdisk | - | - |
| VI | - | Cylinder | - | - |
| VII | - | Reciprocating holder | - | - |

**Release profile comparison[10,14-16]**

Under certain conditions it can be used as a surrogate for the assessment of bioequivalence.

A model is mathematical description of a biologic system and is used to express quantitative relationships.

1) Theoretical basis
2) Empirical equation

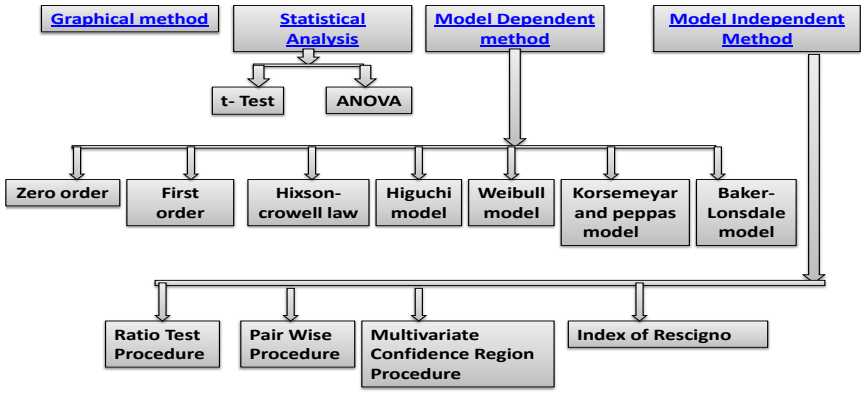



**Fig.2.Different methods for comparison of release profile**

Methods used to compare dissolution data are

**Statistical methods[10,14-16]:**

1.Exploratory data analysis method.
2.Repeated measures design.
3.Multivariate approach (MANOVA: multivariate analysis of variance).

**Regression model:**

Statistical optimization designs have been previously documented for the formulation of many pharmaceutical dosage forms. Several types of regression analysis are used to optimize the formulation from in vitro release study.

1. Linear or first order regression model.
2. Quadratic model or second order regression model
3. Non linear regression models.

**Model dependent methods[6,17-19]:**

**Zero order**

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_o - W_t = K_o t$$

$$W = K_o t$$

Where,

Wo = initial amount of drug in the pharmaceutical dosage form at time t

Wt = amount of drug in pharmaceutical dosage form at time t
W = amount of total drug release
$K_o$ = proportionality constant or zero order release constant
The pharmaceutical dosage forms following this profile will release the same amount of drug in a unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

**First order**
This type of model to analyze drug dissolution study was first proposed by Gibaldi (1967) and later by Wagner (1969). The model describe relationship between drug release and time.

$$Q_t/Q_\infty = k_1t^{1/2} + k_2t$$

Where,
$Q_t$ = amount of drug released in time t
$Q_\infty$ = initial amount of drug in the solution (normally it is zero)
$K_1$ = first order release rate constant
The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in it's interior, in such way, that the amount of drug released in unit time diminishes.

**Hixson-Crowell**
Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of it's volume, derived an equation that can be described in the following manner:

$$W_o^{1/3} - W_t^{1/3} = K_{hc}t$$

Where,
$W_o$ = initial amount of drug in pharmaceutical dosage form at time t
Wt = remaining amount of drug in pharmaceutical dosage form at time t
$K_{hc}$ = constant incorporating the surface volume relation.
This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface. When this model is used, then release rate is limited by the drug particle dissolution rate and not by the diffusion that might occurs through the polymeric matrix. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.

**Higuchi**
In the matrix systems, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on rate of solid dissolution. Higuchi equation developed by Higuchi can be represented as:

$$Q_t = K_Ht^{1/2}$$

Where,

Qt = amount of drug released at time t
$K_H$ = Higuchi release rate constant
This model is useful when drug released from the matrix is diffusion controlled. However, when applying them to controlled drug delivery system, the assumptions of the Higuchi equation kept in mind :

- The initial drug concentration in the system is much higher than the solubility of drug.
- Mathematical analysis is based on one dimentional diffusion.
- The suspended drug is in fine state such that the particles are much smaller in diameter than thickness of the system.
- Swelling or dissolution of polymer carrier is negligible.
- The diffusivity of the drug is constant.
- Perfect sink conditions are maintained.

**Korsmeyer- peppas**
Korsmeyer et al (1983) developed a simple semi empirical model, relating exponentially, the drug released to the elapsed time (t):

$$Q_t/Q_\infty = K_kt^n$$

Where,
$Q = Q_t/Q_\infty$ = fractional release of drug
$K_k$ = constant incorporating structural and geometric characteristic of the drug dosage form.
n = release exponents, indicative of drug release mechanism and the function of t.
Peppas (1985) used this n value in order to characterize different release mechanisms.

**Table.2.Interpretation of diffusion release mechanisms from polymeric films**

| Release exponents (n) | Drug transport mechanisms | Rate as a function of time |
|---|---|---|
| 0.5 | Fickian diffusion | $t^{-0.5}$ |
| 0.5 < n < 1.0 | Anomalous transport | $t^{n-1}$ |
| 1 | Case II transport | Zero order release |
| Higher than 1 | Super case II transport | $t^{n-1}$ |

**Weibull**

The general empirical equation described by Weibull (1951) was adapted to the dissolution or release process.

$$m = 1- \exp[-(t-Ti)^b/a]$$

Where,
m = accumulated fraction of drug
Ti = lag time before the onset of dissolution or release processes and most of cases will be zero.
a = time scale of the process
b = shape parameter
To pharmaceutical systems following this model, the logarithm of the dissolved amount of drug versus the logarithm of time plot will be linear.

**Hopfenberg**

The release of drug from surface eroding devices with a several geometries was analyzed by Hopfenberg who developed a general mathematical equation describing drug released from slabs, spheres and infinite cylinders displaying heterogenious erosion.

$$M_t/M_\infty = 1- [1-k_o t/C_o a_o]$$

Where,
Mt = amount of drug dissolved in time t
$M_\infty$ = total amount of drug dissolved
$M_t /M_\infty$ = fraction of drug dissolved
$k_o$ = erosion rate constant
$C_o$ = initial concentration of drug in matrix
$a_o$ = initial radius for a sphere or cylinder or the half thickess for the slab.

**Model independent methods[3,6,14,18-20]:**

Model independent methods are now gaining more popularity in the pharmaceutical industry to compare the dissolution profiles of test and reference, which is required at the time of submission to US FDA for approval of generic drugs. Model independent methods to compare the dissolution profiles are again differentiated into: ratio tests and pair wise procedures, Difference factor ($f_1$), Similarity factor ($f_2$), Dissolution efficiency, Mean dissolution time (MDT).

**Difference Factor ($f_1$)**

Difference factor focuses on the difference in percent dissolved between reference and test at various time intervals. It can be mathematically computed by using.

$$f_1 = \left\{\left[\sum_{t=1}^{n}|R_t - T_t|\right] \Big/ \left[\sum_{t=1}^{n} R_t\right]\right\} \times 100$$

**or**

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} x100$$

The factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product. The percent error is zero when tests and reference profiles are identical and increase proportionality with the dissimilarity between the two dissolution profiles. US FDA included the $f_1$, $f_2$ factors in various guidance documents and stated different criteria's for dissolution profile comparison as.

-The dissolution profiles can be compared only when number of dissolution units used are equal to or greater than 12. The similarity factor should be computed from the average mean dissolution data of 12 units. The mean data for comparison can be used only if the coefficient of variation at the first time point is NMT 20%, and NLT 10% at the rest of time intervals.

-For accurate calculation of similarity factor, statistical approach of establishment of confidence intervals, to determine whether the reference and test are statistically significant or not may be used.

In general, to ensure similarity between the profiles, $f_1$ should be in the range of 0-10. To calculate the fit factors, the mean dissolution profiles from the both profiles at each time interval were used.

**Similarity Factor ($f_2$)**

The similarity factor is a logarithmic reciprocal square root transformation of one plus the average means squared differences in percent dissolved between the test ($T_t$) and reference ($R_t$) products over all time points (n). It stresses on the comparison of closeness of two comparative formulations. The US FDA and EMEA suggests that two dissolution profiles are declared similar if $f_2$ is between 50 to 100. It can be computated using the formula.

$$f_2 = 50\log\left\{\left(1+\frac{1}{n}\sum\left(R_t - T_t\right)^2\right)^{-0.5} x100\right\}$$

where,

n = number of dissolution sample times.

$R_t$ and $T_t$ = individual or mean percent dissolved at each time point t, for the reference and test dissolution profiles, respectively.

The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases. This factor is endorsed by the FDA as acceptable and preferred method for dissolution profile comparison. The main advantage of $f_2$ equation are that it is easy to compute and provide a single no. to describe the comparison of dissolution profile data.

To evaluate of similarity between dissolution is based on following parameters:

- Minimum of three dissolution time points are measured.
- Number of drug product tested for dissolution is 12 for both test and reference.
- Not more than one mean value of > 85% dissolved for each product.
- Standard deviation of mean of any product should not be more than 10% from the second to last dissolution time points.

**LITERATURE REVIEW**[16,17,21-24]

**Nilufer Yuskel, *et al* (2000)** had used different comparison methods to dissolution profiles of immediate release commercial film coated tablets of naproxen sodium in order to evaluate each methods in terms of easy application and usefulness. The applied methods for the comparison of in vitro dissolution profiles are ANOVA based methods, model dependent methods and model independent methods including difference factor, $f_1$ and similarity factor, $f_2$. Difference factor seems to be easier to apply and interpret; only one value is obtained to describe the closeness of the two dissolution profiles.

**Paulo Costa, *et al* (2001)** had studied drug release from solid dosage form is developed or produced, it necessary to ensure that drug dissolution occurs in an appropriate manner. The drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of time, t. Some are model dependent and some are model independent can be used to characterize release profiles or dissolution.

**A. Prior, *et al* (2004)** had performed comparison of therapeutic performance of two medicinal products containing the active substance is critical means of assessing the possibilities of alternative using between an essentially similar medicinal products. A study is basically a comparative study designed to establish equivalence between test and reference products.

**Esra Demlrttrk *et al* (2005)** had employed comparison method in evaluating scale-up and post-approval changes such as manufacturing site changes, component and composition changes, equipment changes and process changes. Two point specifications are suggested for characterizing the quality of drug product and for accepting product sameness under SUPAC – relating changes. In the presence of certain minor changes the single point dissolution test may be adequate to ensure unchanged product quality and performance. For more major changes a dissolution profile comparison performed under identical conditions for the product before and after the changes is recommended. Dissolution profiles may be considered similar by virtue of overall profile similarity and similarity at every dissolution sample time point.

**D. Samaha, *et al* (2009)** was shows generic drugs offer a cost-effective alternative to brand name products. However, the main concern with modified-release formulations is the substitution of one product for another. Accordingly, the first objective of this study was to assess the interchangeability of the available diltiazem extended-release (ER) products on the basis of their in vitro dissolution characteristics using USP Apparatus 2 and 3.The second objective was to compare dissolution profiles in simulated fasted and fed states and determine whether there is a change in the mechanism of drug release. Dissolution profiles characterized using Apparatus 2 or 3 under fasted conditions were similar.

**Kassaye L. *et al* (2013)** was explained different methods which can be used to compare dissolution profile data. In this study the two most important and widely engaged methods have been used: the fit

factors and dissolution efficiency (D.E.). The fit factors can be expressed by two approaches: difference factor, $f_1$ and similarity factor, $f_2$.

The second comparison method employed in this was dissolution efficiency (D.E.) model. The calculation were made for each individual vessel. Thus, the mean D.E. > for each brand with it's 95% confidence interval was obtained and compared by measuring the difference between the mean D.B. the test brands.

**NEED AND OBJECTIVES[7,14]**

**Needs-**

-Dissolution is critical step for performance of a drug as well as dosage form, because it is a prerequisite for drug absorption.

-To differentiate between formulations and to evaluate the potential effect of formulation and other process variable on drug bioavailability.

-To ensure bioequivalence from batch to batch

-To ensure that preparation complies with product specification, as it is requirement for regulatory approval of marketing for the registered product.

-Vital component of overall quality control progamme

-To predict the performance of the preparation under in vivo conditions.

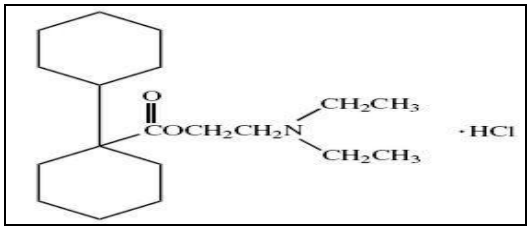
**Objective-**

In the development of solid dosage forms, an ehical or proprietary product, which has been available in market and established its efficacy clinically, is usually selected as reference. The generic preparation is always prepared with its dissolution profile as closely similar as possible to that of the proprietary product. Hence it was decided to compare the release of two marketed formulations to predict the performance of the preparation under in vivo conditions.

**DRUG AND TABLET PROFILE[4,7,11,13,17,25-33]**

**Dicyclomine Hydrochloide**

The name Dicyclomine hydrochloride was formely used in united kingdom




| |
|---|
| Syn - Dicycloverine Hydrochloride, Dicycloverini Hydrochloridum |
| IUPACName-2(-diethylamino)ethylbicyclohexyl-1carboxylate hydrochloride |
| CAS No. – 77-19-0 |
| Mol Formula- $C_{19}H_{35}NO_2$.HCl |
| Mol Weight- 345.9 |

***Description-*** A white or almost white, Crystalline Powder, odourless or almost odourless. It has a bitter taste. Crystal from butanone. It shows polymorphism.
Solubility- Soluble in water, freely soluble in alcohol, chloroform, very slightly soluble in ether and in methylene chloride.

Melting Point (m.p.) – 164°- 165° C
pH= 5.0-5.5
Log p value – 5.5
Aq. Solubility – 3.2703 g/L
Pka – 8.96
Class- tertiary amine, Synthetic compound.

***Pharmacodynamics-*** dicyclomine is an anticholinergic drug, a medication that reduces the effect of acetylcholine, a chemical released from nerve that stimulate the muscle by blocking receptors for acetylcholine on smooth muscles. It also has direct relaxing effect on smooth muscles. Dicyclomine is used to treat or prevent spasm in the muscles of the gastrointestinal tract in the irritable bowel syndrome. In addition gastrointestinal propulsive motility and decrease gastric acid secretion and control excessive pharyngeal, tracheal and bronchial secretions.

***Mode of action-*** action is achieved via a dual mechanism (1) a specific anticholinergic effect (antimuscarinic) at the acetylcholine receptors and (2) a direct effect upon smooth muscle (musculotropic).

***Metabolism –*** metabolized in liver by cytochrome P450.
Volume of distribution- 3.65 L/Kg
Protein binding - > 99%

***Elimination -*** principle route of elimination is via the urine 79.5 % of the dose. Excretion also occurs in the feces, but to a lesser extent (8.4 %).

***Use-*** Antispasmodic, Antiemetic

***Limit-*** It contains not less than 99% and not more than 101% of dicyclomine hydrochloride, calculated either reference to the dried substance.
storage- Store protected from light

**Dicyclomine Hydrochloride Tablet**
Synonym- Dicycloverine Hydrochloride Tablet

***Limit-*** Dicyclomine Hydrochloride tablet contains not less than 92.5% and not more than 107% of the stated amount of dicyclomine hydrochloride, $C_{19}H_{35}NO_2$.HCl

***Dissolution-***
Medium: 0.01 N Hydrochloride; 500 ml
Apparatus No. : 2
Speed: 50 rpm
Time: 45 min
Direction – Take this medication 30 min before meals, avoid alcohol.

***Storage-*** preserve I well closed containes.

## MATERIALS AND METHODS[32]

### Materials

The uncoated tablet of Dicyclomine Hydrochloride tablet was purchased from local market. The labelled amount of drug substance is 20 mg per Tablet.

### Methods

**Preparation of 0.01 N HCl :**
Solution of 0.01 N may be prepared by diluting 0.85 mL to 1000 mL with water

**Preparation of standard stock solution**
10 mg of Dicyclomine Hydrochloride was weighed accurately and dissolved it in 100 mL of 0.01 N HCl in 100 mL of volumetric flask. Concentration of stock solution is 100 µg/mL.

**Preparation of standard calibration curve for Dicyclomine Hydrochloride using 0.01 N HCl**
From the above standard stock solution 0.5, 0.1, 0.15, 0.2, 0.25 mL were withdrawn and transferred to 10 mL volumetric flask and make up the volume upto 10 mL with 0.01 N HCl to get concentration of 5, 10, 15, 20, 25 µg/mL respectively. The absorbance of each solution was measured by UV-Visible Spectrophotometer at 400 nm and 0.01 N HCl as blank. The curve of concentration (x axis) Vs. absorbance (y axis) was plotted.

**In vitro release profile**
Dissolution Studies on test (Cyclopam) and reference (Cyclohot) tablets of Dicyclomine Hydrochloride were conducted in USP Apparatus 2 i.e. Paddle Apparatus (Elecrolab, Mumbai) with triplicate set for each brand. The dissolution medium was 500 ml of 0.01 N HCl. The paddle rotation speed was kept at 50 rpm for 60 minutes. Samples were analysed by UV-Visible spectrophotometry at 400 nm. (Shimadzu UV- 160 A, Japan). Percentage of drug dissolved from the tablet was calculated.

## RESULTS

**Table.3.Absorbance of Dicyclomine Hydrochloride in 0.01N HCl**

| S.No. | Concentration (µg/mL) | Absorbance |
|---|---|---|
| 1 | 5 | 0.1174 |
| 2 | 10 | 0.1374 |
| 3 | 15 | 0.1779 |
| 4 | 20 | 0.1918 |
| 5 | 25 | 0.2321 |

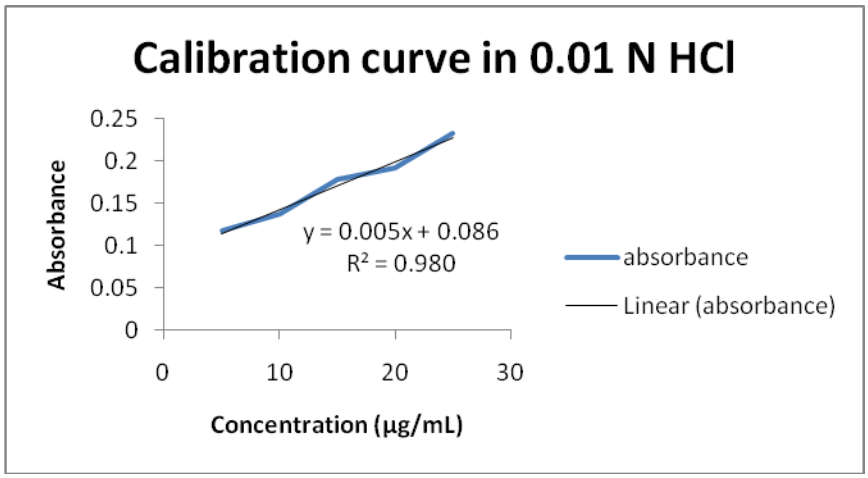



**Fig.2.Graph of Concentration versus Absorbance**

**Table.4.Absorbance of dissolved content of Dicyclomine hydrochloride tablet**

| Time | Absorbance of dissolved content of dicyclomine hydrochloride tablet | | | | | |
|---|---|---|---|---|---|---|
| | Cyclohot tablet | | | Cyclopam tablet | | |
| | Tab 1 | Tab 2 | Tab 3 | Tab 1 | Tab 2 | Tab 3 |
| 5 | 0.1101 | 0.1005 | 0.1234 | 0.1032 | 0.112 | 0.1321 |
| 10 | 0.1398 | 0.1364 | 0.1549 | 0.1328 | 0.1375 | 0.1439 |
| 15 | 0.1567 | 0.1545 | 0.1776 | 0.1667 | 0.1745 | 0.1777 |
| 20 | 0.1947 | 0.1829 | 0.1945 | 0.1885 | 0.2231 | 0.2006 |
| 30 | 0.2115 | 0.2133 | 0.2231 | 0.2174 | 0.2432 | 0.231 |
| 40 | 0.2502 | 0.2478 | 0.2534 | 0.2485 | 0.2638 | 0.2521 |
| 50 | 0.2602 | 0.2561 | 0.2532 | 0.2645 | 0.2714 | 0.2713 |
| 60 | 0.2738 | 0.2816 | 0.2761 | 0.2884 | 0.2847 | 0.2904 |

**Table.5.Percent release for dicyclomine hydrochloride tablet**

| Time | % Release obtained for dissolved content of dicyclomine hydrochloride tablet | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | % Release for cyclohot tablet | | | Av. % Release | % Release for cyclopam tablet | | | Av. % Release |
| 5 | 12.05 | 7.75 | 18.7 | 12.8333 | 8.6 | 13.5 | 23.05 | 15.05 |
| 10 | 27.141 | 25.855 | 34.824 | 29.2733 | 23.572 | 26.52 | 29.411 | 26.501 |
| 15 | 36.129 | 35.419 | 46.863 | 39.4703 | 40.99 | 45.545 | 46.89 | 44.475 |
| 20 | 55.836 | 50.314 | 56.229 | 54.1263 | 52.697 | 70.74 | 59.257 | 60.898 |
| 30 | 65.323 | 66.493 | 71.614 | 67.81 | 68.172 | 82.171 | 75.603 | 75.3153 |
| 40 | 85.928 | 85.026 | 88.135 | 86.363 | 85.172 | 94.053 | 87.603 | 88.9427 |
| 50 | 92.57 | 90.804 | 89.709 | 91.0277 | 94.661 | 99.641 | 98.864 | 97.722 |
| 60 | 101.112 | 105.265 | 102.831 | 103.069 | 108.396 | 108.155 | 110.267 | 108.939 |

**Table.6.Acceptance criteria for dissolution**

| Stage | No. of units | Acceptance criteria |
|---|---|---|
| $S_1$ | 6 | Each unit is not less than Q* +5% |
| $S_2$ | 12 | Average of 12 units ($S_1$ + $S_2$) is not less than Q* and each unit is less than Q - 15% |
| $S_3$ | 12 | Average of 24 units ($S_1$ + $S_2$+$S_3$) is not less than Q - 15% |

A value is often considered satisfactory and is an excellent goal since a common dissolution tolerance in the USP/NF is Not less than 75% dissolved and in the IP is not less than 70% in 45 min.

**Table.7.Kinetic modeling for dissolution profile**

| Marketed Tab | Equation and R2 | Modeling for dissolution of dicyclomine Tablet | | | | | |
|---|---|---|---|---|---|---|---|
| | | Zero order | First Order | Hixson-crowell's | Higuchi | Korsmayer's Peppas | |
| X Axis | | Time | Time | Time | Sqrt Time | Log Time | |
| Y Axis | | % Release | LOG% CDR | Cube Rt of drug remain | % Release | LOG% CDR | Release Exponent (n) |
| Cyclohot 1 | Equation y= | 1.605x + 13.35 | -0.02x + 2.091 | -0.027x + 2.723 | 16.67x - 24.59 | -1.01x + 2.855 | |
| | R2 | 0.951 | 0.982 | 0.99 | 0.987 | 0.833 | |
| | K | 2.2733 | 0.2585 | 0.1468 | 10.93 | 1.3002 | -1.01075 |
| Cyclohot 2 | Equation y= | 1.702x + 8.897 | -0.025x + 2.199 | -0.031x + 2.823 | 17.62x – 31.08 | -1.204x + 3.081 | |
| | R2 | 0.963 | 0.893 | 0.973 | 0.995 | 0.7 | |
| | K | 2.0826 | 0.2593 | 0.1484 | 10.385 | 1.2863 | -1.20403 |
| Cyclohot 3 | Equation y= | 1.449x + 21.94 | -0.02x + 2.042 | -0.026x + 2.625 | 15.09x + 12.53 | -0.981x + 2.784 | |
| | R2 | 0.948 | 0.95 | 0.977 | 0.99 | 0.805 | |
| | K | 2.6571 | 0.2529 | 0.1424 | 12.1276 | 1.272 | -0.98185 |
| Cyclopam 1 | Equation y= | 1.742x + 10.17 | -0.029x + 2.244 | -0.048x + 3.087 | 18.05x – 30.82 | -1.365x + 3.237 | |
| | R2 | 0.964 | 0.883 | 0.825 | 0.996 | 0.679 | |
| | K | 2.1929 | 0.2558 | 0.144 | 10.8675 | 1.2491 | -1.36532 |
| Cyclopam 2 | Equation y= | 1.677x + 18.78 | -0.033x + 2.233 | -0.035x + 2.74 | 17.73x – 22.49 | -1.365x + 3.237 | |
| | R2 | 0.887 | 0.907 | 0.977 | 0.955 | 0.732 | |
| | K | 2.5683 | 0.245 | 0.1404 | 12.3691 | 1.1547 | -1.61469 |
| Cyclopam 3 | Equation y= | 1.594x + 20.53 | -0.027x + 2.155 | -0.048x + 3.001 | 16.45x - 16.64 | -1.309x + 3.117 | |
| | R2 | 0.967 | 0.941 | 0.825 | 0.992 | 0.743 | |
| | K | 2.7706 | 0.2475 | 0.137 | 12.605 | 1.209 | -1.30909 |

**Table.8.Calculation for difference factor and similarity factor**

| S.No | Time | $R_j$ | $T_j$ | $R_j - T_j$ | $(R_j - T_j)^2$ |
|---|---|---|---|---|---|
| 1 | 5 | 15.05 | 12.8333 | 2.2167 | 4.913759 |
| 2 | 10 | 26.501 | 29.2733 | 2.7723 | 7.685647 |
| 3 | 15 | 44.475 | 39.4703 | 5.0047 | 25.04702 |
| 4 | 20 | 60.898 | 54.1263 | 6.7717 | 45.85592 |
| 5 | 30 | 75.3153 | 67.81 | 7.5053 | 56.32953 |
| 6 | 40 | 88.9427 | 86.363 | 2.5797 | 6.654852 |
| 7 | 50 | 97.722 | 91.0277 | 6.6943 | 44.81365 |
| 8 | 60 | 108.939 | 103.069 | 5.87 | 34.4569 |
| | SUM= | 517.843 | 483.973 | 39.4147 | 225.7573 |

| $F_1$ | $F_2$ |
|---|---|
| 7.611322351 | 52.94365818 |

**Table.9.Standard values for $F_1$ and $F_2$**

| Standard Values | |
|---|---|
| $F_1$ RANGE | $F_2$ RANGE |
| 0 – 10 | 50 - 100 |

Where,

$F_1$ = Difference factor
$F_2$ = Similarity factor
$R_j$ = percent dissolved of reference at each time point j.
$T_j$ = percent dissolved of test at each time time point j.
N = Sampling No.
$W_j$ = optional weight factor

## DISCUSSION

The *$f_1$* factor is easy to apply as compare to kinetic modeling; only one value is obtained for comparing two dissolution profiles. Dissolution profile follows Higuchi and Hixson – Crowell model while the f1 and f2 value were obtained are in the range. These methods present an acceptable model approach to the true relationship between percent dissolved and time variables. These methods provide detailed information about dissolution profile.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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