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A Study on Drug Release Kinetics of Fexofenadine Hydrochloride and Montelukast (Monti-FX) Tablets with Application of Mathematical Models and Evaluation of their Bioactivity

K. MrudulaDevi [1*,2], S. Satyaveni [2], G. PurnachandraRao [3]

[1*,2]Research Scholar in Chemistry, JNTUniversity, Kakinada-533003, A.P. India. Associate Professor, Department of Freshmen Engineering,Aditya University,Surampalem-533437, India

[2]Department of Chemistry, JNTUniversity, Kakinada-533003, A.P. India

[3]Department of Chemistry, JNTUniversity, Kakinada-533003, A.P. India

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KEYWORDS

Drug, Kinetics, Order, Model,Bioactivity .

ABSTRACT:

The aim of the present proposed research work is to use mathematical models to studythe drug release kineticsin tablet matrix. A research is carried out using Fexofenadine and Montelukast tablets, 120 mg/10 mg.Drug release profile is carried in Hexane and Phosphate bufferin the time intervals of 0,10,20,30,45,60 and 75hoursrespectively.Toget a better idea about the drug release kinetics, numerous mathematical models, including the Zero order, First order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas have been proposed. The high degree of correlation coefficient between the drug release profiles of fexofenadine and montelukast tablet serves as the basis for selecting the best model. Additionally, it has been determined that the medication release pattern of Fexofenadine and Montelukast, is best fitted withZero order model and follows Zero order drug release kinetics in both hexane and phosphate buffer. The bioactivity of the drug has also been evaluated against gram-positive, gram-negative bacterial species and fungal species and found activity in combined form of Mont-FX.

1. Introduction

Mathematical models minimize the number of experiments needed to deepen the understanding by designing different conditions for predicting the physical and chemical drug release mechanism. The precise experimental settings needed to fit parameters in mathematical models, which often utilized in drug delivery sector, offers low predictability [1-2]. While these models are applicable for various conditions which are useful in model based design of release profiles.Strong acid present in the medium serves as the external source of the acid catalyst, or it mayproduced internally [3]. Small or porous microspheres may swiftly experience the diffusion of acidic breakdown products, reducing internal pH heterogeneities and erosion brought on by autocatalysis [4-5]. Similarly other drug degradation and drug release conditions can also be affected by such factors.By utilising appropriate mathematical techniques, it is simpler to acquire the right numbers for the quantitative study of drug release from any dose form for designing of new drug delivery system, prediction of drug release rate, optimization of the release kinetics, drug transport mechanism [6-19]as a function of characteristics of some dosage form for the improvement of therapeutic efficacy and safety of the drug. With the use of empirical testing, Bolisetti et al.[20] determined that release of repaglidine from floating gels of cubosomes follows Higuchi's rule. Al-Kady et al. similarly assumed a Higuchi model in their release analyses of coumarines [21]. The study of Caccavoindicates that some models are prevailing in the order Peppas model 30%, Higuchi model 19.4%, of Zero Order model with 18.9%, and First Order model with 15.6%, and Hixon-Crowell model 7.8% of usage frequency [22].The dissolution profile is described by many mathematical functions that form the foundation of model-dependent approaches. The generated model parameters are used to evaluate the dissolution profiles [23-24]. Researchers studied the bioactivity of

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727

antihistamine, Leukotriene receptor antagonist class of drugs which can signifies the present studies on Fexofenadine and Montelukast tablets [25-28].

Fexofenadine ($C_{32}H_{39}NO_4$.HCl) is an antihistamine drug for the treatment of allergic rhinitis and chronicurticaria. Therapeutically As a selective peripheral H1 antagonist, fexofenadine blocks histamine from activating the H1receptors, hence alleviating allergy-related symptoms. Consequently, compared to other antihistamines that easily traverse the blood-brain barrier, is less likely to make you sleepy. Additionally, fexofenadine doesn't have any impact on the alpha 1 or beta adrenergic receptors, anticholinergic, antidopaminergic, or dopaminergic systems.

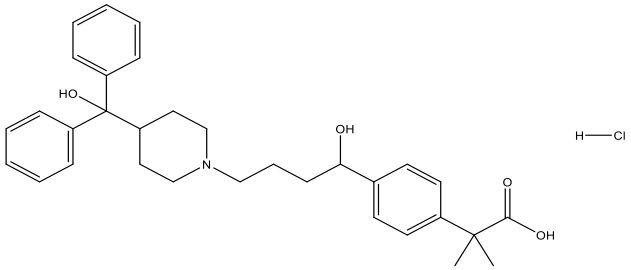

Fig-1: Structure of Fexofenadine

Montelukast($C_{35}H_{36}ClNO_3S$) used in maintenance treatment of asthma, allergic rhinitis, hives and urticarial of long duration. Therapeutically montelukast is leukotriene receptor antagonist (cysteinylleukotriene receptor). It is also be used as an adjunct therapyinsymptomatictreatment of mastocytosis.

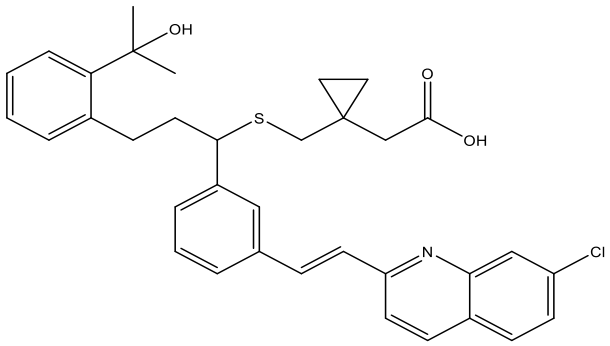

Fig-2: Structure of Montelukast

Fexofenadine (FEX), is a highly selective peripheral histamine H1-receptor antagonist and Montelukast (MKT) is a selective leukotriene D4 receptor antagonist that is used as an antiasthmatic. Both drug moieties show potential drug activities. In the present research it is proposed to study the kinetics of the degradation products of the FEX and MKT individually in various aqueous solution with change in pH, under thermal and light along with the solubility studies. So far these were not formulated in the combination and the research results helpful in the utilization these drugs in combination.

EXPERIMENTAL

Drugrelease kinetic studies

a) Zero order model[29]

C_0-C_t =K_0tand Ct=C0+K0t

Where C_t = Drug released (at time t), C_0=Initial drug concentration and K_0= zero-orderconstant.

Plot was drawn between Cumulative drug releaseandTime.

a) ***First order model***[29]

DC/dt=-K_1C

Where,

K_1= first order rate constant

The first order process follows linear kinetics.

Integral equation,

log C=log C_0-K_1t/2.303

Where K_1= First order rate equation, C_0= Initial drug concentration, C = Remaining % drug

Plot was drawn between drug remaining *vs.* time.

b) Higuchi model: Prominent kinetic equation to evidence the drug dissolution studies in drug delivery development[29-30].

Q =A \

Where,

Q = cumulative amount of drug released, C_O= initial concentration of drug, C_S= drug solubility

D = diffusion coefficient of drug molecule in the matrix.

With the help of this expression, it is simple to investigate the release of a drug through a porous system[31].

Journal of Chemical Health Risks

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$Q = \sqrt{(D\delta/\tau)(2C-\delta C_S)C_{st}}$

Where D = diffusion coefficient of drug molecule in solvent; δ = porosity of the matrix and

t= tortuisity of the matrix and after simplifying the above equation

Higuchi equation: $Q=K_H \times t_{1/2}$

Where,

K_H= Higuchi dissolution constant.

Cumulative drug release % Vs Square root of timewas plotted.

c) Korsmeyer-peppas model: Diffusion regulated by the Higuchi plot serves as the primary mechanism for drug release. Following this form of diffusion, drug release occurs [32-33]. The Korsmeyer and Peppasmodel was applied forthe data to deduce the dissolving mechanisms.

$M_t/M_\infty=Kkpt$

M_t/M_∞: fraction of drug released at time t,$Log(M_t/M_\infty)=log\ Kkp+nlogt$,

Where,

M_t=drug released (in time t)

$M\infty$ =drug released (after ∞ time)

n=drug release exponent

Kk_p= Korsmeyer release rate constant.

Graph was plotted between log Cumulative drug release %$log(M_t/M_\infty)$ *vs*log time (log t).

***d) Hixson-crowell model*:** A relation between release of drug with respect to timeisgivenbyequation[32-38].

$$W_0^{1/3} - W_t^{1/3} = K_t HC$$

Where, $\sqrt{D\ (2C_O - C_S)C_{st}}$

W_0= initial quantity of drug ,W_t=residual amount

K_tHC = Hixson-Crowell constant.

Plotted between Cubethroot of remaining drug %*vs*Time.

Interpretation of the drug release profile of fexofenadine and montelukast tablet has been done by applying Zero, First order, Higuchi,Korsmeyer –Peppas and Hixson-Crowell models.

Bioactivity:

Determination of Minimum Inhibitory Concentration(MIC)

The antibacterial activity of the Fexofenadine and Montelukast has been assessed byusing dilution technique for the determination of MIC. The gram positive bacteria*bacillus,staphylococcus* and gram negative bacteria *E.coli,klebsiella, pseudomonas* strains are selected for evaluation of antimicrobial activity. The drug is dissolved in DMSO solvent with different concentrations and tested for antifungal activity, by employing an agar- agar media for the growth of fungal culture of *fussariumoxysporum* and *sclerotium*by placing in the centre of the plate and incubated at 30±2 ^{0}C for 24 to 96 hours and the inhibition percentage (IP%) was calculated.

RESULTS AND DISUSSION

The details of pharmaco-kinetic parametric values of Fexofenadine and Montelukast in hexane and phosphate bufferare summarizedin Tables-1and 2

Zero order model: The plot represents the Fexofenadine and Montelukast cumulative drug release % against time confirms the principle of zero order release kinetics which can be explained based on correlation coefficient r^2. In hexane r^2=0.9489 for Fexofenadine and r^2=0.9627 for Montelukast where as in phosphate buffer r^2=0.9805 for Fexofenadine and r^2=0.9781 for Montelukast which indicates the mathematical model fallows Zero order in both the cases.

***First order model*:** The plot represents the Fexofenadine and Montelukast cumulative drug release % against time reports that it does not met the criteria of first order release kinetics due to lower correlation coefficient r^2 value.In hexane r^2=0.9488 for Fexofenadine, r^2=0.9507 for Montelukast, In phosphate buffer r^2=0.8033 for Fexofenadine, r^2=0.8216 for Montelukast).

Higuchi model: Plot represents the Fexofenadine and Montelukastcumulative drug release % against time reports that drug release from matrix was not in agreement with Higuchi model as lowest value of correlation coefficient r^2. In hexane r^2=0.7797 for Fexofenadine and r^2=0.9259 for Montelukast, In

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JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727

phosphate buffer r^2=0.9627 for Fexofenadine and r^2=0.9657 for Montelukast.

Korsmeyer-peppas model: Diffusion exponent or release exponent was observed with larger than 0.89, indicates Super case II transport mechanism for the drug release from the system, according to figures [Figures 1(d), 2(d), 3(d), and 4(d)]. From these figures, the slope of the plot was determined[35].

***Hixson-crowell model*:** Itcan be employed to analyse the drug release profile of 120 mg/10 mg Fexofenadine and Montelukast tablets (Table-1 and Table-2), and assessment is done through a graph[Fig 1(e) - 3(e), 4(e)]. It depicts how diameter of the tablets and the surface area vary as the matrix gradually dissolves over time[36].

Mathematical models will be applied to study the drug release profile in hexane well as in phosphate buffer and interpreted based on graphical presentation and also for evaluation by using correlation coefficient (r^2) which arereported in Table-3. Since the correlation coefficient highest degree decides the mathematical model which follows drug release kinetics[37], abovementionedmathematical models as explained in Table-3 and on comparison of the drug release profiles,itis observed that zero order model show the correlation coefficient (r^2) higher than the other models in both the drugs. Hencethe drug release profile of Fexofenadine and Montelukast Tablets followed the Zero order mathematical model.

Drug Release Mechanisms: Dependingon n which is the release exponent, the transport mechanism of drug and the rate as a function of time can be explained. According to Equation of Korsmeyer-Peppas power law when the value "n" for the kind of diffusion is more than 0.89, it indicates that drug is being released from system and follows the Super Case II transport mechanism[38].In the present study the mechanism involved in Fexofenadine and montelukast, the value of n is higher than 0.89 which clearly confirms the drug transport mechanisms Super Case II Transport and the rate as t^{n-1}.

TheFexofenadine and Montelukast tabletsexamined for Antibacterial activity to find out the MIC by taking the sample in different concentrations100µg/ml,200µg/ml,300µg/ml and 400µg/ml respectively and evaluated against *Pseudomonas,klebsiella, Bacillus, E.coli* and *Staphylococcus.*

The drug molecule sample with concentration 100µg/mlexhibited MIC maximum on *E.coli*(1.0) and very marginally equivalent MIC value on *klebsiella*(0.9), *bacillus*(0.9)&*staphylococcus* (0.9) fallowed by minimum MIC value (0.8) on *pseudomonas.*The drug molecule sample with concentration 200µg/ml exhibited MIC maximum on *E.coli*(1.2) and very marginally equivalent MIC value on *klebsiella*(1.1)*& bacillus*(1.1) fallowed by *staphylococcus* (1.0) and minimum MIC value (0.9) on *pseudomonas.*The drug molecule sample with concentration 300µg/ml exhibited MIC maximum on*bacillus*(1.4) and very marginally equivalent MIC value on *klebsiella*(1.3) &*E.coli*(1.3) fallowed by *staphylococcus* (1.1) and minimum MIC value (1.0) on *pseudomonas.*The drug sample with concentration 400µg/ml exhibited MIC maximum on *klebsiella*(1.8) and very marginally equivalent to MIC value on *E.coli*(1.6),*bacillus*(1.5) &*pseudomonas*(1.4) and minimum MIC value (1.2) on *staphylococcus.*The photographs related to bacterial species with MIC are presented in figures 5(a)-5(e).

TheFexofenadine and Montelukast tablets were evaluated for Antifungal activity to find out the inhibition concentration(IP%) by taking the sample with different concentrations *viz.*,100µg/ml, 200 µg/ml, 300 µg/ml and 400 µg/ml respectively against *fussariumoxysporum* and *sclerotium* fugal species.

The drug sample exhibited maximum IP with 45% Antifungal activity against *fussariumoxysporum*with a concentrationof400µg/mlfallowed by 42%, 38% and 32% IP values with concentrations of300µg/m,200µg/ml and 100µg/ml respectively. But the drug sample has not exhibited any Antifungal activity against *sclerotium*fugal species.

Conclusion

In the present research work the drug release mechanism in Fexofenadine and Montelukasttablets has been explained by various mathematical models like Zero order, First order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas .The release of drug is found to be the best fitted in Zero order model and the dissolution data has beendrawn as per Hixson–Crowell model whichdescribesthe change in diameter, surface area of

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727

the tablets and also with the progressive dissolution as a function of time. The sort of diffusion was estimated by the release exponent (n) value, which is larger than 0.89 which wasconfirmed by Korsmeyer-Peppas power law equation. This is an indication that the medication has been released from the system through the Super Case II transport mechanism.The MIC values confirmed maximum antibacterial activity of the drug Monti-FX against *E-coli*with concentration of 100µg/mland 200µg/ml. It is exhibited antibacterial activity against *Bacillus* with a concentration of 300µg/ml and with 400µg/mlit has potential activity on *klebsiella*.The drug Monti-FX exhibited maximum antifungal activity against*fussariumoxysporum*at a concentration of 400µg/ml but the drug exhibited moderate activity at concentration of 300µg/mlfallowed by 200µg/ml.But it has shown lower activity of 32% with a concentration of 100µg/ml. But surprisingly the Monti-FX drug has not shown any activity against the species*Sclerotium.*

Conflict of Interest

The authors declare that they have no conflict of interest

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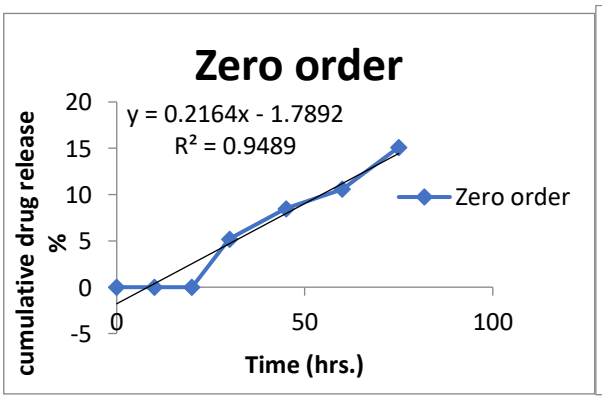
Table-1: Drug release kinetics in Hexane

Time (Hr)	Cumulative drug release %	Drug remaining %	log Cumulative drug remaining %	log time	log Cumulative drug release %	Drug release %	Square root of time	Cubeth Root of drug remaining % (Wt)	W_0-W_t
Fexofenadine									
0	0.00	100.00	2.000	0.000	0.000	100.00	0.000	4.642	0.000
10	0.00	100.00	2.000	1.000	0.000	100.00	3.162	4.642	0.000
20	0.00	100.00	2.000	1.301	0.000	100.00	4.472	4.642	0.000
30	5.20	94.80	1.977	1.477	0.716	5.20	5.477	4.560	0.082
45	8.50	91.50	1.961	1.653	0.929	3.30	6.708	4.506	0.054
60	10.60	89.40	1.951	1.778	1.025	2.10	7.746	4.471	0.035
75	15.12	84.88	1.929	1.875	1.180	4.52	8.660	4.395	0.076
Montelukast									
0	0.00	100.00	2.000	0.000	0.000	100.00	0.000	4.642	0.000
10	10.20	89.80	1.953	1.000	1.009	10.20	3.162	4.478	0.164
20	16.50	83.50	1.922	1.301	1.217	6.30	4.472	4.371	0.271
30	20.40	79.60	1.901	1.477	1.310	3.90	5.477	4.302	0.340
45	24.93	75.07	1.875	1.653	1.397	4.53	6.708	4.218	0.424
60	30.98	69.02	1.839	1.778	1.491	6.05	7.746	4.102	0.540
75	45.24	54.76	1.738	1.875	1.656	14.26	8.660	3.797	0.845

Graphical representation of Zero order, Higuchi model of drug release of fexofenadine are presented in Fig-1(a) and 1(b) respectively.



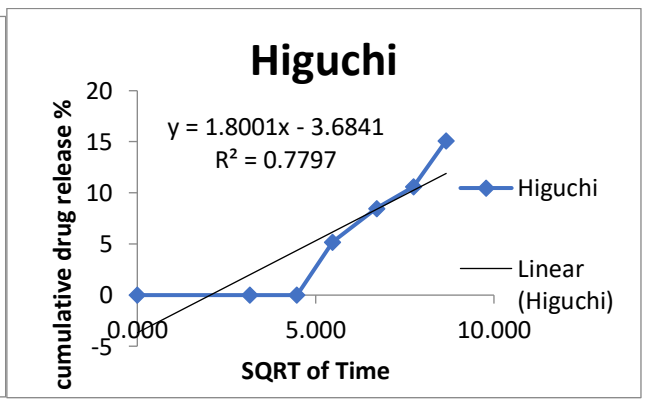


Fig-1(a): Zero order model (FEX) Fig-1(b): Higuchi model (FEX)

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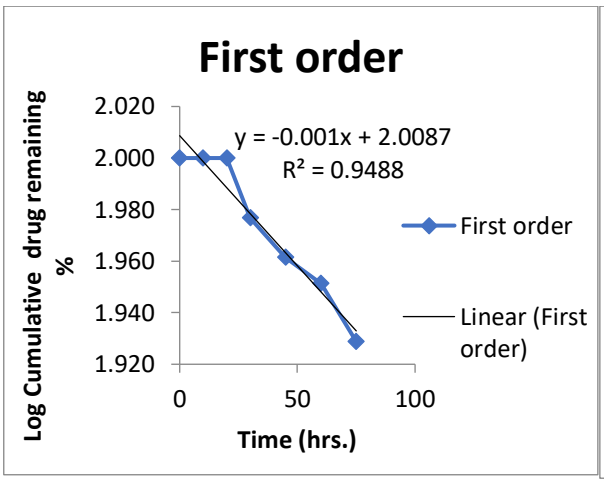
Graphical representation of First order and Kors-peppas model of drug release of fexofenadine are presented in Fig-1(c) and 1(d) respectively.



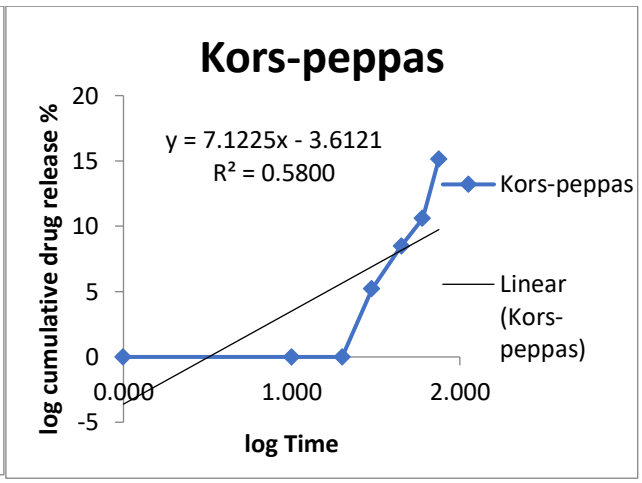


Fig-1(c): First order model (FEX) Fig-1(d): Korspeppas model (FEX)

Graphical representation of Hixson model of drug release of fexofenadine is presented in Fig-1(e).

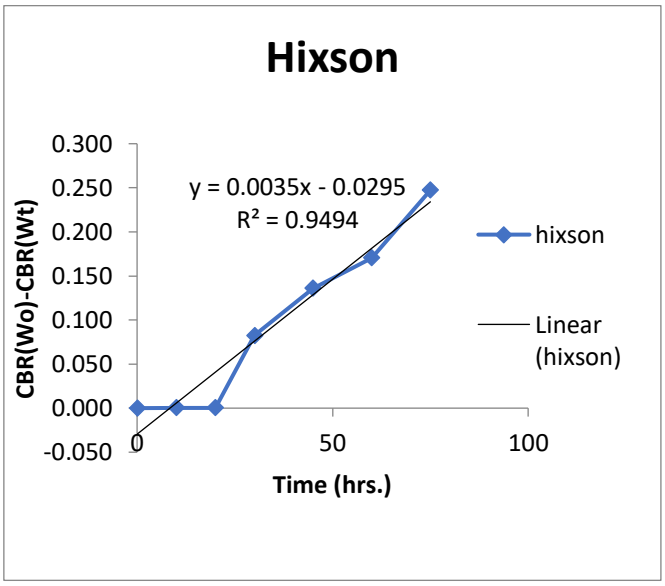


Fig-1(e): Hixson model (FEX)

Graphical representation of Zero order, Higuchi model of drug release of Montelukast are presented in Fig-2(a) and 2(b) respectively.

Journal of Chemical Health Risks
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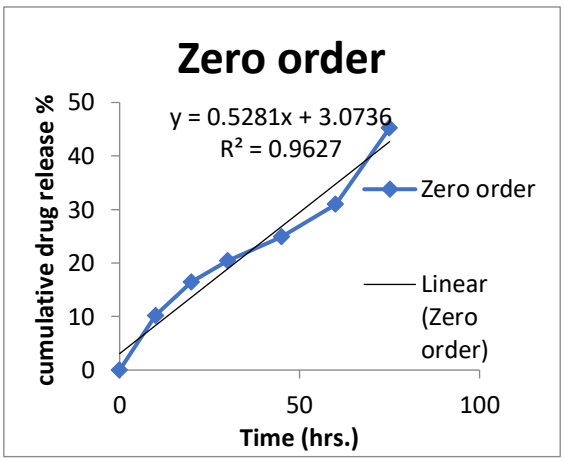
JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727



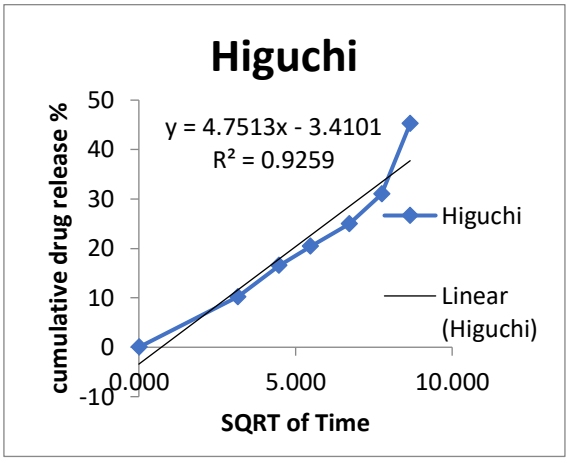
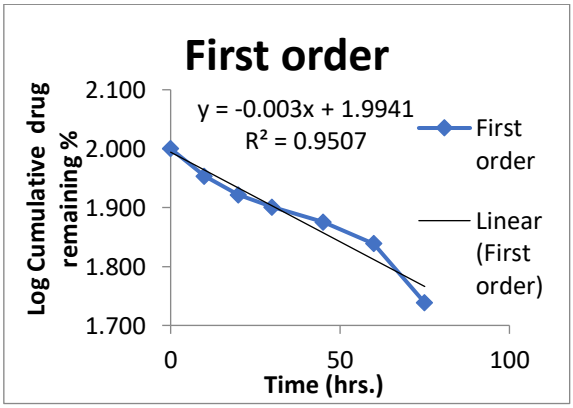


Fig-2(a): Zero order model (MNT) Fig-2(b): Higuchi model (MNT)

Graphical representation of First order, Kors-peppas model of drug release of Montelukast are presented in Fig-2(c) and 2(d) respectively.



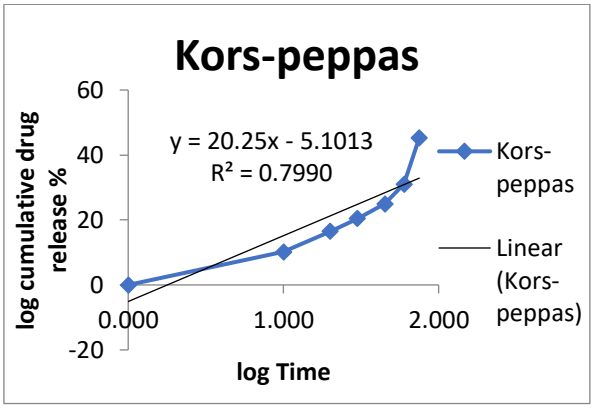


Fig-2(c): First order model (MNT) Fig-2(d): Kors-peppas model (MNT)

Graphical representation of Hixson model of drug release of Montelukast is presented in Fig-2(e).

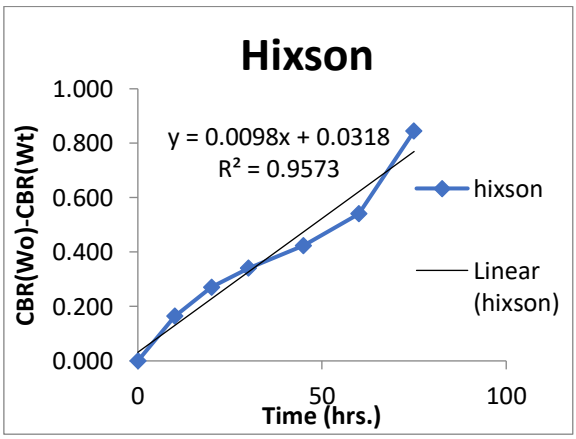


Fig-2(e): Hixson model (MNT)

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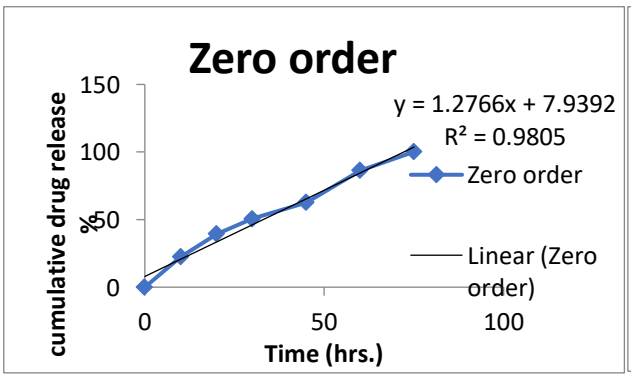
JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727

Table- 2:Drug release kineticsin Phosphate buffer

Time (Hr)	Cumulative drug release %	Drug remaining %	log Cumulative drug remaining %	log time	log Cumulative drug release %	Drug release %	Square root of time	Cube Root of drug remaining % (Wt)	W_0-W_t
Fexofenadine									
0	0.00	100.00	2.000	0.000	0.000	100.00	0.000	4.642	0.000
10	22.56	77.44	1.889	1.000	1.353	22.56	3.162	4.262	0.380
20	39.41	60.59	1.782	1.301	1.596	16.85	4.472	3.928	0.714
30	50.67	49.33	1.693	1.477	1.705	11.26	5.477	3.668	0.974
45	62.77	37.23	1.571	1.653	1.798	12.10	6.708	3.339	1.303
60	86.34	13.66	1.135	1.778	1.936	23.57	7.746	2.390	2.252
75	100.20	-0.20	0.000	1.875	2.001	13.86	8.660	-0.585	5.227
Montelukast									
0	0.00	100.00	2.000	0.000	0.000	100.00	0.000	4.642	0.000
10	25.62	74.38	1.871	1.000	1.409	25.62	3.162	4.206	0.436
20	40.80	59.20	1.772	1.301	1.611	15.18	4.472	3.897	0.745
30	49.58	50.42	1.703	1.477	1.695	8.78	5.477	3.694	0.948
45	64.91	35.09	1.545	1.653	1.812	15.33	6.708	3.274	1.368
60	88.35	11.65	1.066	1.778	1.946	23.44	7.746	2.267	2.375
75	101.20	-1.20	0.000	1.875	2.005	12.85	8.660	-1.063	5.705

Graphical representation of Zero order, Higuchi model of drug release of fexofenadine are presented in Fig-3(a) and 3(b) respectively.



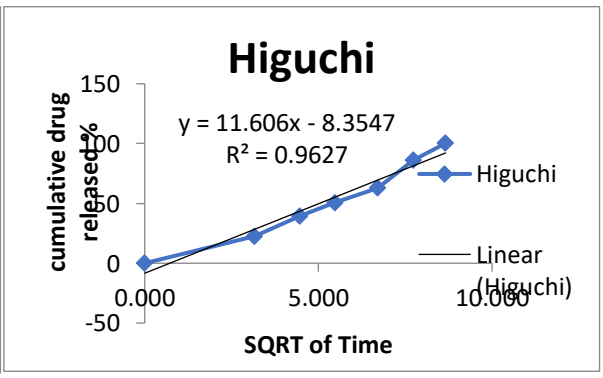
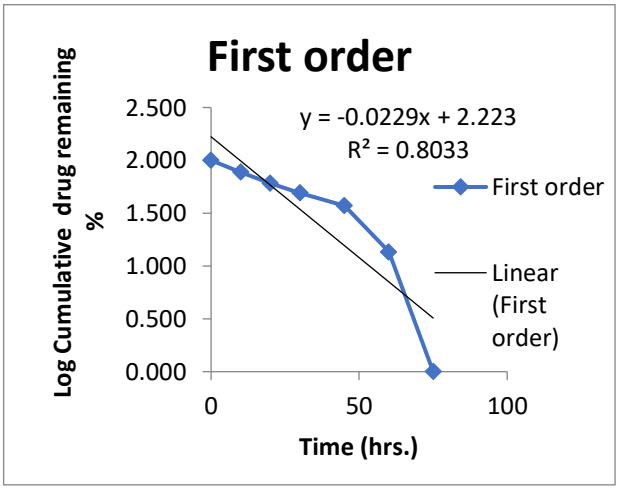


Fig-3(a): Zero order model (FEX) Fig-3(b): Higuchi model (FEX)

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727

Graphical representation of First order, Kors-peppas model of drug release of fexofenadine are presented in Fig-3(c) and 3(d)respectively.



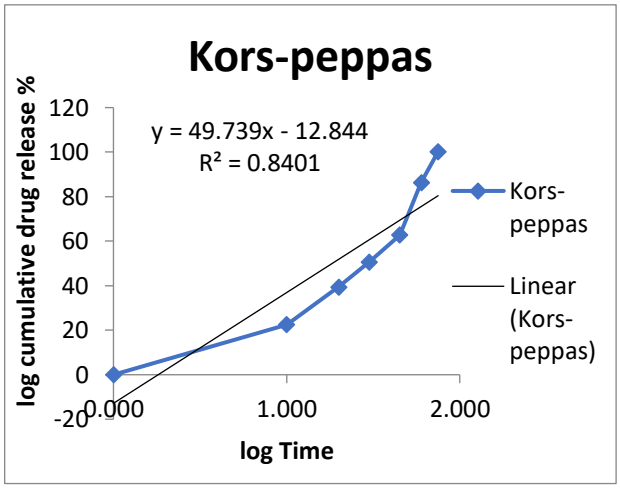


Fig-3(c): First order model (FEX) Fig-3(d): Kors -peppas model (FEX)

Graphical representation of Hixson model of drug release of fexofenadine is presented in Fig-3(e)respectively

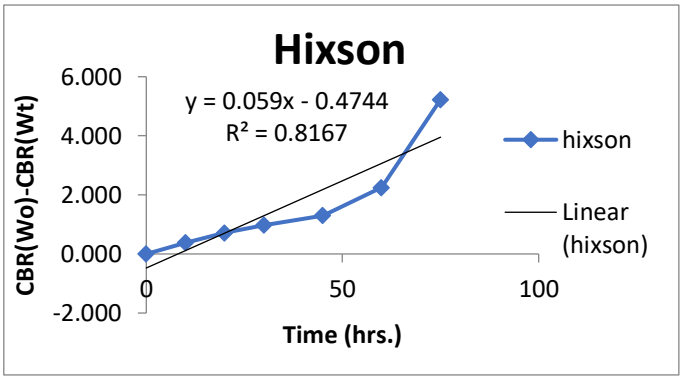
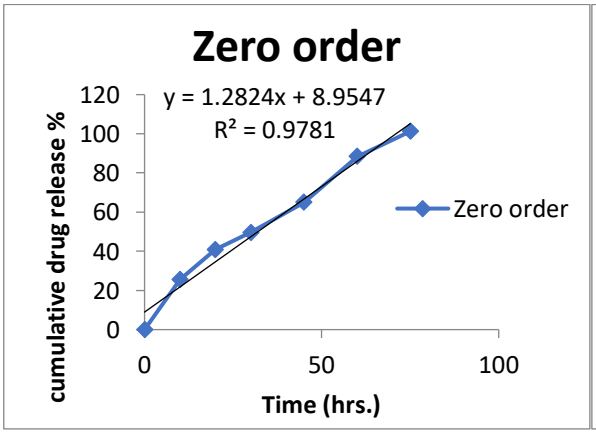


Fig-3(e): Hixson model (FEX)

Graphical representation of Zero order, Higuchi model of drug release of Montelukast are presented in Fig-4(a) and 4(b) respectively.



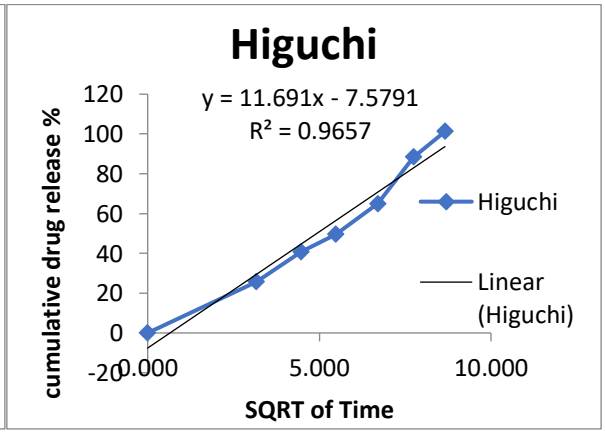


Fig-4(a): Zero order model (MNT) Fig-4(b): Higuchi model (MNT)

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727

Graphical representation of First order, Kors-peppas model of drug release of Montelukast are presented in Fig-4(a) and 4(b)respectively.

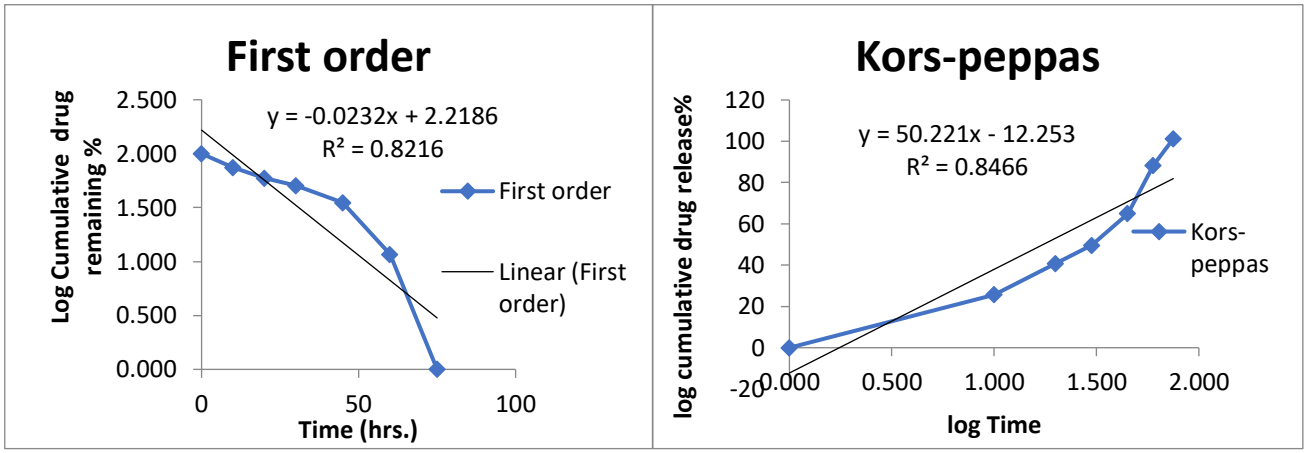


Fig-4(c): First order model (MNT) Fig-4(d): Kors-peppas model (MNT)

Graphical representation of Hixson model of drug release of Montelukast is presented in Fig-4(e).

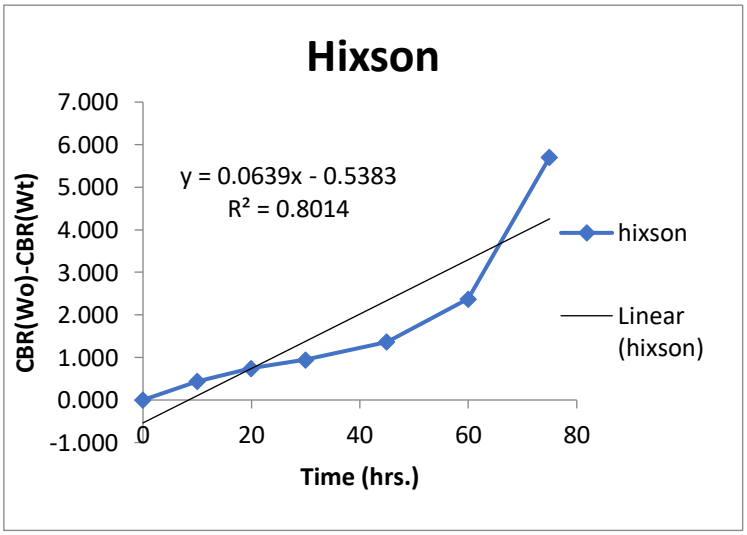


Fig-4(e): Hixson model (MNT)

The value of $r^2$and the details related to the slope and intercept are presentedin Table-3.

Table 3: r^2,slope and intercept of graphs in mathematical models

Model Name	Fexofenadine			Montelukast		
	r^2	Slope	Intercept	r^2	Slope	Intercept
In Hexane						
Zero order	0.9489	0.2164	-1.7892	0.9627	0.5281	3.0736
First order	0.9488	-0.0010	2.0087	0.9507	-0.0030	1.9941

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727

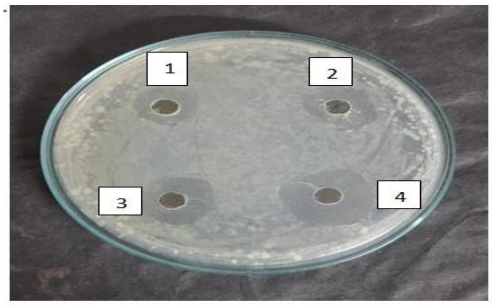
Higuchi	0.7797	1.8001	-3.6841	0.9259	4.7513	-3.4101
Korsmeyer -Peppas	0.5800	7.1225	-3.6121	0.7990	20.2500	-5.1013
Hixson-Crowell	0.9494	0.0035	-0.0295	0.9573	0.0098	0.0318
In phosphate buffer						
Zero order	0.9805	1.2766	7.9392	0.9781	1.2824	8.9547
First order	0.8033	-0.0229	2.2230	0.8216	-0.0232	2.2186
Higuchi	0.9627	11.6060	-8.3547	0.9657	11.6910	-7.5791
Korsmeyer –Peppas	0.8401	49.7390	-12.844	0.8466	50.2210	-12.2530
Hixson-Crowell	0.8167	0.0590	-0.4744	0.8014	0.0639	-0.5383

Bioactivity Evaluation:

a) Antibacterial activity:Thedetails of Antibacterial activity of Monti-FX has been summarized in Table-4

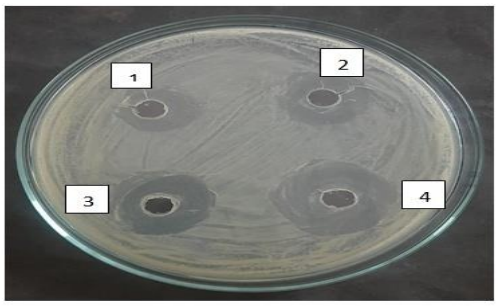
Table-4: Antibacterial activity of Fexofenadine and Montelukast tablets

Sample	**Pseudomonas (cm)**	**Klebsiella (cm)**	**Bacillus (cm)**	**E.coli (cm)**	**Staphylococcus (cm)**	**Activity Order**
100µg/ml	0.8	0.9	0.9	1.0	0.9	*E.coli>(bacillus,klebsiella&staphylococcus)> pseudomonas.*
200µg/ml	0.9	1.1	1.1	1.2	1.0	*E.coli>(klebsiella&bacillus)>staphylococcus>pseudomonas.*
300µg/ml	1.0	1.3	1.4	1.3	1.1	*Bacillus>(klebsiella&E.coli)>staphylococcus> pseudomonas.*
400µg/ml	1.4	1.8	1.5	1.6	1.2	*Klebsiella>E.coli>bacillus>pseudomonas> staphylococcus.*



Pseudomonas

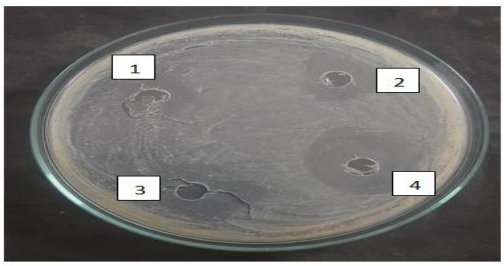
Fig-5(a)



Klebsiella

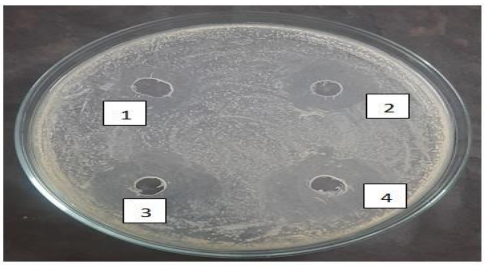
Fig-5(b)

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(4), 1874-1887 |ISSN:2251-6727



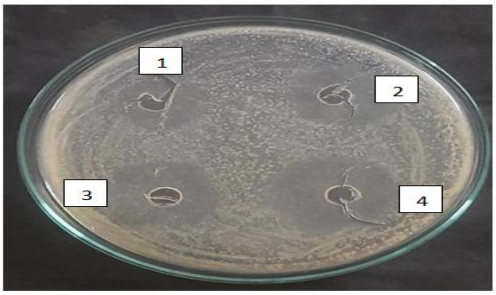
E coli

Fig-5(c)



Staphylococcus

Fig-5(d)



Bacillus

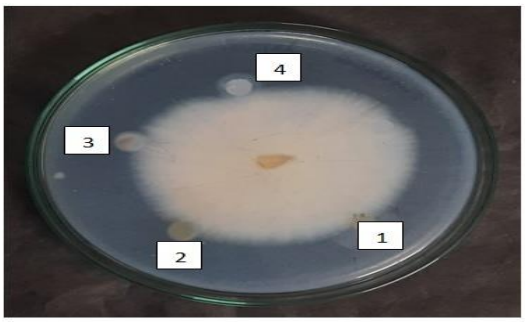
Fig-5(e)

b)*Antifungal Activity*:Thedetails of Antifungal activity of Monti-FX has been summarized in Table-5.

Table-5: Antifungal activity of Fexofenadine and Montelukast tablets.

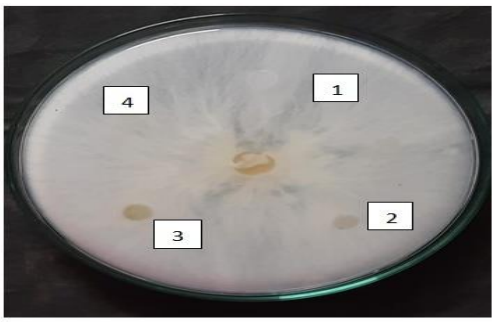
Cocentrations	**100µg/ml**	**200µg/ml**	**300µg/ml**	**400µg/ml**
Fussariumoxysporum	32%	38%	42%	45%
Sclerotium	0%	0%	0%	0%

The photographs related to fungal species with MIC are presented in figures 6(a) & 6(b).



Fussarium oxysporum

Fig-6(a)



Sclerotium

Fig-6(b)