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Research Article

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Design and Evaluation of Controlled Release Matrix Tablet of Aspirin by Using Hydrophobic Polymer

Gamal Osman Elhassan

Department of Pharmaceutics, Unaizah College of Pharmacy, Qassim University, Qassim, Kingdom of Saudi Arabia.

ABSTRACT

Controlled-release of aspirin would be useful in the management of arthritis by administering it at bed-time. Moreover, it could be potentially helpful in reducing the gastrointestinal side effects of aspirin. The circadian rhythm of pain, in rheumatoid arthritis (RA), Joint stiffness and pain are more frequent in the morning. Four formulations F1-F4 of controlled release Aspirin were prepared using different concentrations of the polymer ethyl cellulose through direct compression by geometrically mixing method. Namely they are F1, F2, F3 and F4 using 5%, 10%, 15% and 20 % EC respectively. The aim of present study was to study the effect ethyl cellulose concentration on the release profiles of Aspirin. All the prepared tablet formulations showed good tableting characteristics. In this study, the release of all the formulations followed first-order kinetics and the drug was released via anomalous release mechanism. Therefore, diffusion together with erosion were involved in the drug release from these formulations. By using 10% of ethyl cellulose onwards, it was possible to sustain the release of aspirin. By increasing the concentration of the polymer, the rate of drug release from its matrix decreased. In this study, we studied the release for 10 hours. The formulation F1 did not achieve controlled release of Aspirin. More than 80% of Aspirin was dissolved within the first 4 hours. On the other hand, formulation F3 and F4 showed a controlled release for ten hours, with 50.81-64.634% of drug was released. The formulation F2 showed the best dissolution profile for controlled release Aspirin tablets, where it released 88.87% of the drug at the tenth hour. Therefore, formulation F2 was the best formulation for relieving arthritis if administered at or before bed-time compared to formulation F3 and F4.

Keywords: *Aspirin, circadian rhythm, Ethyl-cellulose, Controlled-release and Anomalous-release mechanism.*

INTRODUCTION

The present study was conducted for the formulation and the in-vitro evaluation of Aspirin controlled release matrix tablets using ethyl cellulose as a polymer. The aim of this study was to study the effect of different concentration of ethyl cellulose on the release of Aspirin. The main adverse effect associated with Aspirin is gastrointestinal disturbance and ulcers. Controlled release Aspirin formulation allows less frequent administration and could potentially decrease its side effect [1]. Controlled release Aspirin may be useful for the relief of arthritis as a bed time dose [2].

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder. In rheumatoid arthritis (RA) joint stiffness and pain is more prominent in the morning. An increased pain intensity and sleep disturbance is observed during the night and early morning [3]. In RA, Aspirin is a commonly prescribed NSAID. The common dose used is 325-650 mg four to six times daily [4]. Aspirin can be given up to 3g a day in RA patients. However, the dosing has to be adjusted according to their gastrointestinal capability.

Therefore, controlled release of Aspirin that extends its release for 8-10 hours has the potential to be therapeutically

beneficial in rheumatoid arthritis. Figure 1 shows the chemical structure of Aspirin or Acetylsalicylic Acid (ASA). The chemical name of Aspirin is 2-Acetoxybenzoic acid. Its molecular formula is C9H8O4 and has a molecular weight of 180.15742 g/mol.

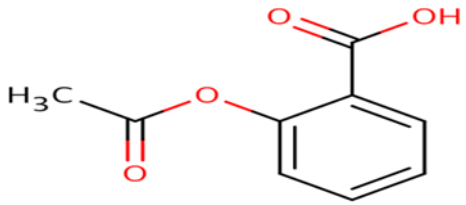


Figure 1 Structure of Aspirin

Aspirin is a non-steroidal anti-inflammatory agent which is prescribed to alleviate mild to moderate pain. Besides analgesics property, aspirin also has anti-inflammatory property, antipyretic property as well as platelet aggregation inhibition effect. Aspirin can inhibit directly and irreversibly the enzyme cyclooxygenase, both COX-1 and COX-2 to decrease the production of prostaglandins and thromboxanes from arachidonic acid. Other NSAIDS such as ibuprofen and diclofenac sodium are reversible cyclooxygenase inhibitors. Aspirin can donate acetyl group to cyclooxygenase. The non-acetylated salicylates do not have any clinical significance on platelet aggregation.

The irreversible acetylation of cyclooxygenase prevents the synthesis of thromboxane A2 which plays a vital role in platelet aggregation. Since aspirin has many effects as mentioned above, it has been prescribed for the treatment and prevention of many diseases and conditions. As for pain, the use of NSAID has been established as first line for mild to moderate pain.

Aspirin is also prescribed to reduce the inflammation associated with many conditions including rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, systemic lupus erythematosus and many others. Besides that, low dose Aspirin is widely prescribed to prevent blood clot formation due to platelet aggregation in cardiovascular disease patients and patients who have had stroke before. Here, Aspirin works as a blood thinner reducing the risk of stroke and other cardiovascular diseases. The plasma half-life of is approximately 15 minutes. If the dose is increased to 300-625 mg, the half-life increases to 3.1–3.2 hours [5].

Aspirin precipitates in the stomach because it has poor solubility and this may cause GIT side effects. Aspirin is a weak acid and thus it is poorly soluble in acidic medium. With increasing pH, its solubility dramatically increases. Aspirin is slightly soluble in water and its solubility is pH dependent. pH dependency of Aspirin solubility is one of the causes of GIT complication such as ulcers in the presence of acidic gastric juice [6]. Safety is an important factor when prescribing medicines, and in multiple-dosing aspirin has a worse gastric effect than other NSAIDs [7].

Rheumatism has been known since the great river cultures of the Middle East. Clay tablets from the Sumerian period described the use of willow leaves to treat it. The Egyptians also used myrtle or willow leaves for their pain-relieving effects. Edward Stone is recognized as the first one to give a scientific description of the effects of willow bark. In 1763, he wrote a letter to the Royal Society in London, describing treating patients suffering from fever with 20 grains, of powdered willow bark in a drum of water every 4 hours [8].

The results of the present systematic review confirm aspirin's efficacy as a postoperative analgesic. The analgesic dose-response confirms that higher doses give better analgesia. When comparing aspirin with paracetamol, the analgesic effect produced by the two drugs is similar. One gram of aspirin produces the same analgesic effect as one gram of paracetamol [9].

Houde and Wallenstein stressed that with NSAIDs, unlike opioids, it was difficult to show an analgesic dose-response for outcomes such as peak relief. This meta-analysis shows that there is indeed an underlying dose-response, and we used total pain relief. Gastric irritation is the significant adverse effect and 1 patient in 40 will have gastric irritation after the administration of a single dose of aspirin. Another view shows that one elderly person will be admitted with ulcer bleeding per 3000 NSAID prescriptions [10].

When given in-vivo, Aspirin has a short half-life and it is rapidly hydrolyzed by esterases to salicylic acid which is a weak inhibitor of COXs [11]. Aspirin is a low potency antipyretic analgesic with half-life of 15 minutes and has a Tmax of 15 minutes. Aspirin also have a low oral bioavailability [12]. Aspirin irreversible inhibits COX-1 and COX-2. It has a high effect on COX-1 but less effect on COX-2. Since platelets are unable to generate fresh enzymes, a single dose of aspirin is considered sufficient to produce antiplatelet effect for the whole lifetime of thrombocytes. In patients with peptic ulcer,

Aspirin may cause bleeding because of its antiplatelet effect and due to the irritation of the gastrointestinal mucosa [13].
Ethyl cellulose (EC) is hydrophobic polymer and is essentially tasteless, odorless, colorless, physiologically and pharmacologically inert. It has been commonly employed as a Pharmaceutical solid vehicle in preparing microcapsules, coating material and matrix forming material for sustained release dosage forms [14]. Ethyl cellulose was found to be a significant rate controlling polymer which can produce tablets of desired hardness and friability [15].
The use of conventional acetylsalicylic acid (ASA) tablets for chronic salicylate therapy is an accepted and frequently preferred mode of ASA treatment. Usefulness of conventional Aspirin tablets may be limited by problems of achieving and maintaining therapeutic plasma salicylate concentrations [16].
The use of polymer membranes to produce controlled release of an active substance from pellets or tablets is quite common. Ethyl cellulose is an effective rate-controlling polymer which can be used to produce tablets of suitable hardness and friability [15]. Ethyl cellulose (EC) and hydroxypropyl cellulose (HPC) are two polymers with film-forming properties. Membranes made of only EC are insoluble in water and have good mechanical properties, but poor water permeability. These properties allow the release of an active substance to be controlled [17].
EC is insoluble in water, but soluble in many organic solvents [18]. Ethyl cellulose polymers are derived from cellulose, which is naturally occurring polymer, and it contains a basic repeating structure of ß-anhydroglucose units, joined together with acetal linkages.
Ethyl cellulose (EC) is hydrophobic polymer and is essentially tasteless, odorless, colorless and physiologically and pharmacologically inert. It has been widely used as a Pharmaceutical vehicle in preparing microcapsules, coating material and matrix forming material for sustained release dosage forms [14].

MATERIALS & METHODS

Materials

Aspirin was supplied by Hovid Pharmaceutical Company (Hovid Inc, Ipoh, Malaysia) as a gift sample. Ethylcellulose was obtained from Dow Chemical Company (USA). Meanwhile, Microcrystalline cellulose (Avicel PH102), Lactose DC and Disodium hydrogen phosphate was obtained from Hercules Chemicals (Singapore) as a gift sample. Talc and Magnesium stearate were purchased from Peter Greven Asia (Malaysia). Methanol was obtained from J.T. Baker, Netherlands.

Preparation of Aspirin matrix tablets

The controlled release tablets were prepared using direct compression with geometrical mixing on a 10-mm concave punch and die tableting machine (Shanghai, China). The tableting machine was set to give constant hardness.
Various concentrations 5%, 10%, 15% and 20% of different polymers were used. Four formulations F1 to F4 were prepared by using a constant amount of active ingredient (325 mg Aspirin) while varying the composition of the excipients. The hydrophobic polymer used was Ethyl cellulose as shown in Table 1.

Table 1 Composition of Aspirin matrix tablets containing different percentage of ethyl cellulose (EC)

Standard curve of Aspirin

50 mg of Aspirin was weighed accurately and dissolved it in 100 mL of methanol to prepare the stock solution. It was subsequently diluted with distilled water to get solutions with concentrations of 0.035, 0.061, 0.122, 0.244, 0.488 and 0.977 µg/mL.
The absorption was measured using UV-visible spectrophotometer. The wavelength used is 265nm. Distilled water was used as the blank. The readings were then recorded.

EVALUATION OF THE PREPARED ASPIRIN MATRIX TABLETS

Evaluation of physical appearance

The prepared tablets were observed visually for cracking, capping, chipping, and lamination.

Weight variation

For weight variation test, ten tablets were randomly selected from each formulation and was weighed one tablet at a time. The average weight for each formulation was determined USP, 2007 [19]. The percentage weight variation for each tablet was calculated using the following formula:

$$\% \text{ Weight variation} = \frac{\text{Average Weight-Individual Weight}}{\text{Individual Weight}} \times 100$$

Tablets Hardness

Ten tablets were randomly selected from each formulation and its hardness was tested. The average hardness was then calculated.

Thickness and diameter

Diameter and thickness of the tablet was measured using a Vernier caliper. For this evaluation, 10 tablets were randomly selected from each formulation and the thickness and diameter were determined individually. The average value was then determined.

Friability

A sample of 20 tablets were picked and weighed together. These tablets were used to evaluate friability. The tablets were placed in the friability tester and were let to revolve for 100 revolutions at a speed of 25 rotations per minute (RPM), dropping the tablets at a distance of 6 inches in each revolution.

After completing the 100 revolutions, the tables were dedusted and weighed again. Percent friability (%F) was calculated using the following formula:

$$\textbf{\% F} = \frac{\text{Inital weight-Final weight}}{\text{Initial weight}} \text{ x } 100$$

DISSOLUTION STUDY

Dissolution test was performed on 3 tablets from each formulation using the USP dissolution apparatus–II, paddle method (Bombay, India). The speed used was 30 rotations per minute (RPM). Distilled water of 1000 mL was used as the dissolution medium. The test conditions are based USP XXIV method [20].

Samples of 5mL from the dissolution medium were withdrawn using a syringe at the intervals of 0.5 hr, 1 hr and every hour up to 10 hours from all three vessels for all the formulations. They were then placed separately in labeled test tubes. Then, the samples were diluted for 60 times and its absorbance was determined using UV-visible spectrophotometer (Japan) using absorbance wavelength of 265 nm.

The mean absorbance values of the 3 tablets were then converted to drug concentration and the percentage of drug release was plotted.

ANALYSIS OF DRUG RELEASE

Determination of mean dissolution time (MDT)

T50% and mean dissolution time (MDT) were calculated using the plot of percentage of drug release versus time. The mean dissolution time (MDT) was calculated based on the following equation.

$$\text{MDT} = \frac{\int_0^\infty \text{dM (t)}}{\int_0^\infty \text{dM(t)}}$$

Drug Release Kinetics

The drug release kinetics were determined by plotting Zero-order (Cumulative percentage of drug released versus time), First-order (Log cumulative percentage of drug remaining versus time), Higuchi (Cumulative percentage of drug released versus square root of time), Korsmeyer-Peppas (Log cumulative percentage of drug released versus log time) and Hixson-Crowell (Cube root of cumulative percentage of drug remaining versus time).

Statistical analysis

One-way analysis of variance (ANOVA) was used to analyze the drug release data using computer software Statistical Package for the Social Science (SPSS) version 21. In this software, T50% and mean dissolution time (MDT) were analyzed.

From the data analysis using this software, significance difference between formulations were obtained. P values of less than 0.05 were considered significant.

RESULTS & DISCUSSIONS

Evaluation of physical properties of the matrix tablets

Physical characteristics of formulations F1 to F4 are presented in table 2. All the formulation prepared showed a good Pharmaco-technical characteristic. The weight variation of the prepared tablets fell within the limits of ± 5%. The hardness of the tablets was found to be within the acceptable limits.

The acceptable range of hardness of tablet is 5 to 10 Kg force (49.03 – 98.07 N). The friability results of all the formulations were within the limit of F<1% (British Pharmacopoeia, 2008).

Table 2 Results of Pharmaco-technical tests forformulations F1-F4

Formulation Code	Physical Parameters					
	Weight (mg), n = 10		Diameter (mm) n = 10	Thickness (mm) n = 10	Hardness (N) n = 5	Friability (%) n = 20
	Average weight	%CV				
F1	449.5 ± 2.80	0.62	10.1 ± 0.00	4.9 ± 0.02	70.5 ± 1.42	0.5
F2	449.3 ± 3.83	0.85	10.1 ± 0.00	5.0 ± 0.02	69.9 ± 1.18	0.6
F3	449.9 ± 4.2	0.90	10.1 ± 0.00	4.8 ± 0.01	69.5 ± 1.03	0.6
F4	450.5 ± 3.17	0.70	10.1 ± 0.00	4.8 ± 0.01	69.3 ± 1.76	0.7

Evaluation of in-vitro release of drug from matrix tablets

Figure 2 showed the mean percentage of drug release profiles of formulation F1 to F4. The results were plotted using time versus percentage of drug release. The graph showed that by increasing the concentration of EC, there is a decrease in drug release rate. The order of drug release ware F1 (5% EC) > F2 (10% EC) > F3 (15% EC) > F4 (20% EC). The studies had shown that the polymer concentrations were inversely proportional to the rate of drug release in all formulations [21]. Swelling of the tablets were observed during the dissolution test. EC swells and retards drug release when it comes in contact with water. At the beginning, it displays surface erosion which permits initial fast release of the drug.

The release rate then decreases when the external layers of tablet becomes depleted and thus water must penetrate into deeper layers of the tablet to reach the undissolved drug [22]. The retarding effect depends on the viscosity of the polymer, content of polymer and solubility of the drug. When 5% EC was used, the release rate was 20.46% at the 0.5 hour and 90.456% at the 10th hour. When 10% EC was used, the release rate was 11.048% at the 0.5 hour and 88.87% at the 10th hour. When 15% EC was used, the release rate was 6.598% at the 0.5 hour and 64.634% at the 10th hour. Lastly, when 20% EC was used, the release rate was 5.92% at the 0.5 hour and 50.81% at the 10th hour.

When the formulation F1 (5%) of EC used, the release rate was not decreased to an acceptable level. More than 80% of the drug was released as early as 4th hour of the dissolution. On the other hand, when formulation F3 (15%) and formulation F4 (20%) EC used, it showed a prolonged sustained profile where, 80% of the drug is not released at the 10th hour.

The formulation F2 using 10% of EC seems to fulfill the acceptable criteria where, the release rate of the drug has been decreased and at the same time, more than 80% of the drug has been release at the 10th hour. The mean T50% and MDT values are shown in Table 3. The mean T50% for formulations F1, F2, F3 and F4 were 1.78 ± 0.01, 3.41 ± 0.02, 5.60 ± 0.01, 9.01 ± 0.14 hours respectively.

From this, it can be concluded that, when polymer concentration increases, the release of Aspirin from the matrix decreases. P value less than 0.05 were considered as significant. Therefore, the differences between the formulations are considered statistically significant. Figure 2 In-vitro drug release profile of Aspirin from tablets containing different concentrations of Ethyl cellulose (EC), N = 3.

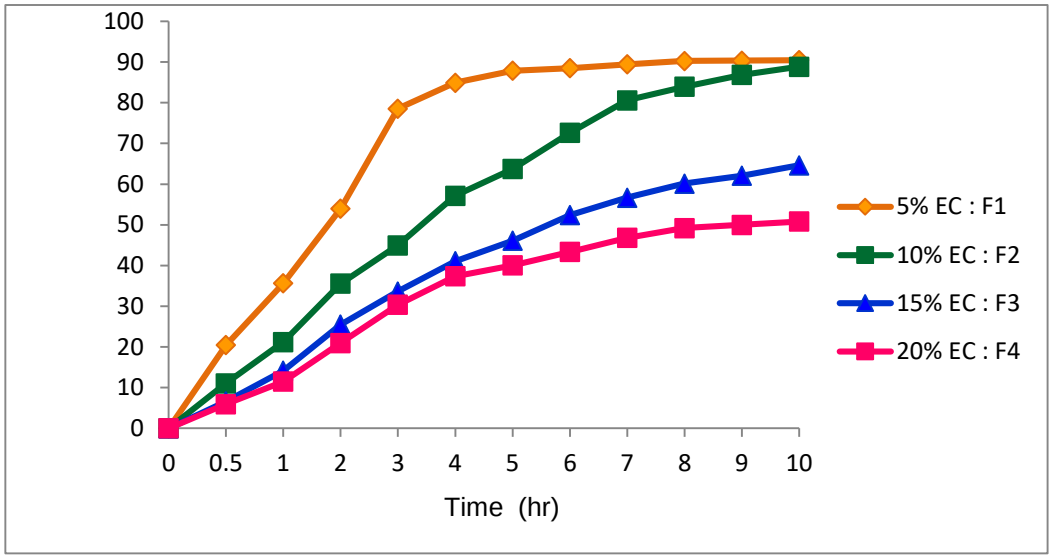


Figure 2 In-vitro drug release profile of Aspirin from tablets containing different concentrations of Ethyl cellulose (EC), N = 3.

Table 3 The mean $T_{50\%}$, MDT and Statistical analysis data of Aspirin tablets containing different concentrations of Ethyl cellulose (EC). N = 3.

Formulation Code	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas	
	r^2	k	r^2	k	r^2	k	r^2	k	r^2	n
F1 (5% EC)	0.712	30.942	0.848	4.206	0.894	8.297	0.819	4.064	0.903	0.487
F2 (10% EC)	0.938	13.138	0.995	4.624	0.987	-6.439	0.991	4.543	0.988	0.692
F3 (15% EC)	0.937	9.0758	0.984	4.545	0.986	-5.150	0.972	4.526	0.978	0.741
F4 (20% EC)	0.896	8.807	0.939	4.523	0.949	-3.045	0.926	4.510	0.969	0.718

Table 4 Kinetics data of Aspirin tablets containing different concentrations of Ethyl cellulose (EC), N = 3.

Formulation Code	$T_{50\%}$ (hours)	MDT (hours)
F1 (5% EC)	1.78 ± 0.01	1.75 ± 0.00
F2 (10% EC)	3.41 ± 0.02	3.35 ± 0.02
F3 (15% EC)	5.60 ± 0.01	3.44 ± 0.00
F4 (20% EC)	9.01 ± 0.14	3.01 ± 0.02
Statistical significance	P < 0.05	P < 0.05

Where, r^2 is the regression coefficient and n is release, or slope exponent.

Table 4 showed regression coefficient and slope exponent of formulations F1, F2, F3 and F4. When the dissolution data was obtained, it was fitted into five kinetic equations. Namely they are Zero-order kinetic equation (Cumulative amount of drug released versus time), First-order kinetic equation (Log cumulative percentage of drug remaining versus time), Hixon-Crowell cube root law kinetic equation (Cube root of cumulative percentage of drug remaining versus time),

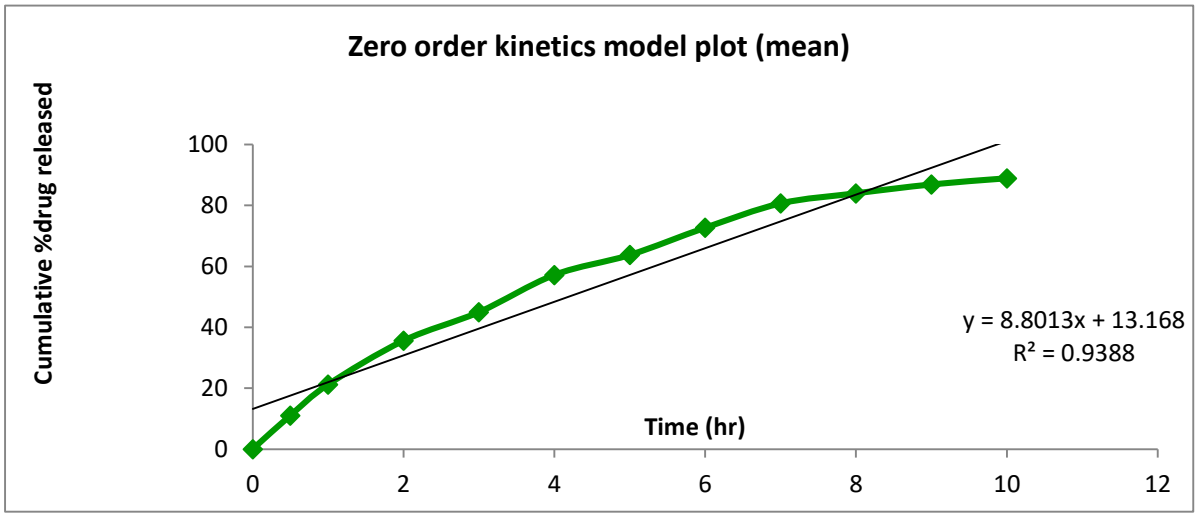
Higuchi square root model of diffusion kinetic equation (Cumulative percentage of drug released versus square root of time), as well as Korsmeyer-Peppas kinetic equation (Log cumulative percentage of drug released versus log time).

From table 4 as well as figure 2, it is evident that the release did not follow zero-order kinetics. The regression value for zero-order is smaller compared to the regression value of first order kinetics for all four formulations. On top of that, the figure 2 shows a curvilinear pattern for all for formulations. In reference to Table 4, the release follows first-order kinetics. This is because; regression value of first-order kinetics is greater than regression value of zero-order kinetics for all four formulations. With first-order kinetic, the dissolution rate is dependent on the concentration of the dissolving species [23]. Besides that, the drug release kinetics were evaluated using Higuchi square root model equation of diffusion as well as Hixson-Crowell equation of erosion. The regression value coefficient obtained from both the equations was compared for all four formulations.

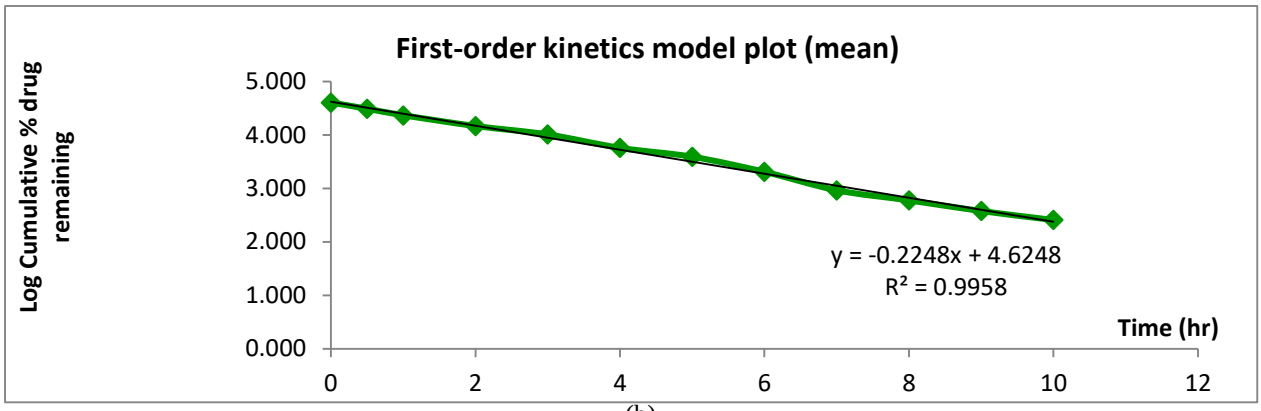
Referring to table 4, formulation F1, F3 and F4, the regression coefficient of Higuchi square root model equation (r^2=0.8945, 0.9869, 0.9492) is higher compared to Hixson-Crowell equation of erosion (r^2=0.8197, 0.9725, 0.9264). This indicates that the release of drug from formulations F1, F3 and F4 was through diffusion mechanism.

However, the regression value of Hixson-Crowell equation of erosion is also high making presence of erosion possible. On the other hand, for F2 the regression value of Hixson-Crowell equation of erosion (r^2=0.9918) is greater compared to Higuchi square root model equation (r^2=0.9876). This indicates that the release of drug from F2 is through erosion mechanism. The situation is vice-versa in F2 compared to the other formulations.

Even though F2 has greater regression value for Hixson-Crowell equation, F2 also has a high regression value for Higuchi square root model equation. Hence, the possibility of diffusion mechanism in F2 is high. Then the results of dissolution tests were further fitted into Korsmeyer-Peppas equation to analyze the diffusion and erosion mechanism of drug release based on the n values. If the n value is less than 4.5, then it is said the release follows Fickian diffusion mechanism. When n value is in-between 4.5 to 8.9, then it follows non-fickian or anomalous mechanism. If the n value is equal to or greater than 8.9, then it follows case II transport. Referring to table 2.8, the n value of all the four formulation is in-between 4.5 to 8.9. The n value for F1, F2, F3 and F4 are 0.4879, 0.6926, 0.7419 and 0.7189 respectively. This is suggesting that all the four formulations are following non-Fickian or Anomalous release mechanism which means there is a combination of both diffusion and erosion mechanisms [24]. Therefore, from the results it can be concluded that the release of Aspirin Controlled release formulation using EC follows first-order release kinetics and the drug was released via Anomalous release mechanism as shown in Fig 3.



(a)



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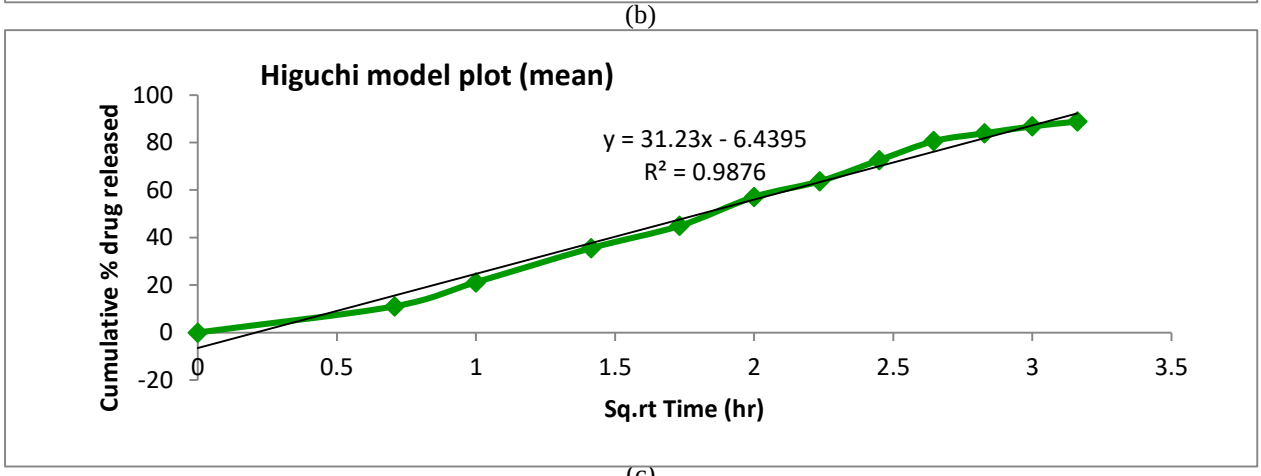

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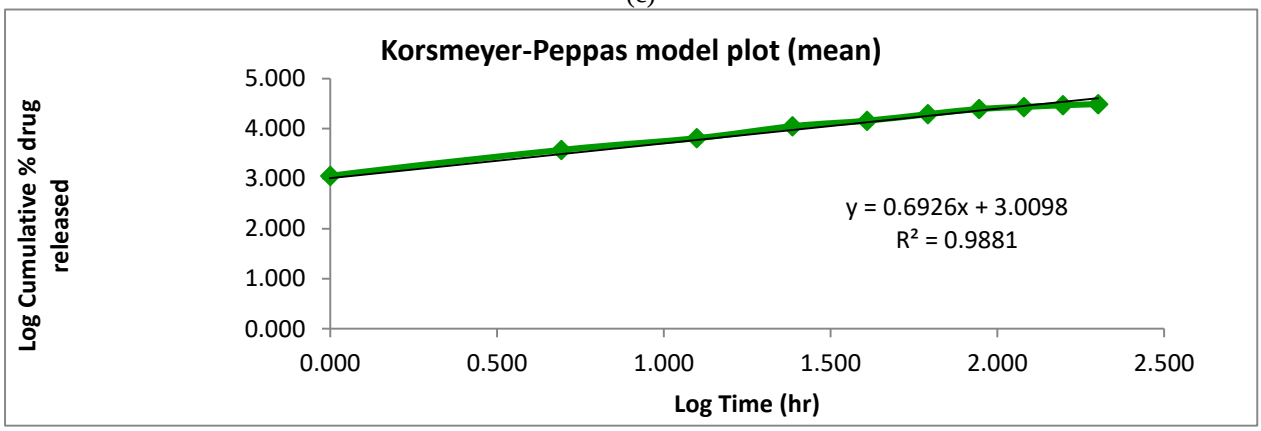

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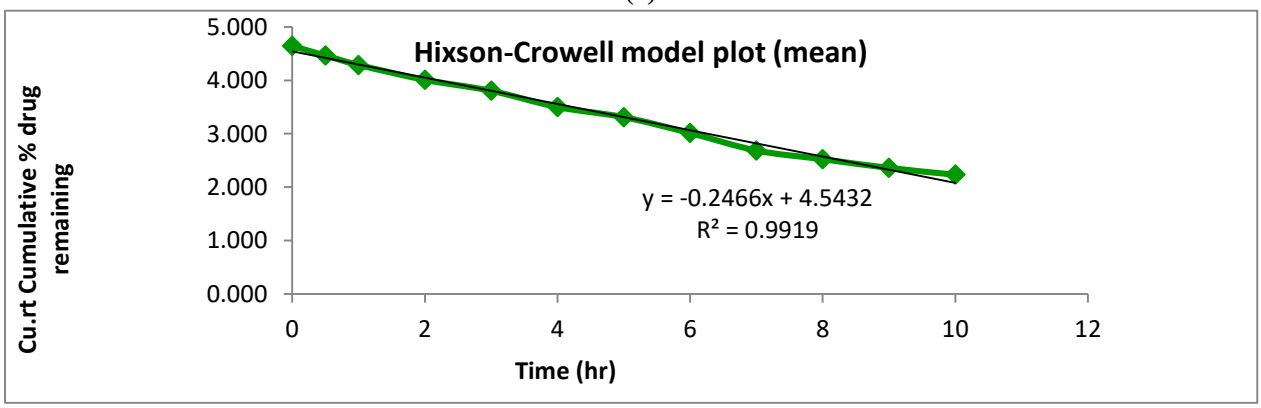

(e)

Figure 3 (a)-(e) Showed kinetic plots of Aspirin release from Formulation F2 (10% EC). Mean, N=3

CONCLUSIONS

All prepared formulations showed good Pharmaco-technical characteristics. The formulations prepared met all Pharmaco-technical parameters including physical appearance, weight variation, thickness, hardness and friability.

From the study conducted, it can be concluded that, use of 10% ethyl cellulose onwards enable to produce a controlled release of aspirin. By increasing the concentration of the polymer, the rate of drug release from its matrix decreases giving a sustained release of the drug. In this study, we are targeting the release of drug for 10 hours. Formulation F1 failed to sustain the release of Aspirin where more than 80% of drug is released within the first 4 hours.

On the other hand, formulation F3 and F4 showed a sustained release for 10 hours with 50.81-64.634% of drug is released from the tablet. Formulation F2 showed the best release profile for 10 hours controlled release Aspirin tablet where it released 88.87% of the drug. Therefore, formulation F2 is the most suitable formulation for the relief of arthritis by dosing before bed-time compared to formulation F3 and F4.

In this study except the formulation F1, all formulations such as F2, F3 and F4 followed first-order release kinetics and the drug was released via Anomalous release mechanism. Therefore, both diffusion and erosion ware present in the release of drug from these formulations.

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