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RESEARCH ARTICLE

Mathematical Modeling of *in vitro* Release Kinetics of Diclofenac Sodium from Complex Coacervates of Irvingia *gabonensis* and Acacia Gums with Gelatin

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ABSTRACT

The study is aimed at comparatively evaluating the in vitro release kinetics of diclofenac sodium from complex coacervates of *Irvingia gabonensis* and acacia gums and gelatin gum using mathematical models. Pre-optimized coacervates and physical admixtures of irvingia / gelatin gums and acacia / gelatin gums were formed at different ratio strengths of 1:2 and 2:1 respectively. Some amounts of the coacervates and physical admixtures equivalent to 500 mg diclofenac sodium were filled into separate hard gelatin capsules. The release profiles of diclofenac sodium from these hard capsule devices were determined spectrophotometrically. The release profiles were compared for similarity by applying the FDA f_2 statistic. The *in vitro* release mechanisms and kinetics were determined by analysis with models like Korsmeyer-Peppas, zero order, first order, Higuchi and Hixon-Crowell Cube-root release models. Results showed that the physical admixtures had their maximum drug release within four hours while the complex coacervates had sustained drug release for more than six hours. The complex coacervates had similar release profiles but their mechanisms of drug release were different and kinetics of drug release followed different mathematical models.

KEYWORDS

Mathematical Modeling, Complex Coacervates, Release Profiles, Kinetics and Mechanisms

INTRODUCTION

Drug release is the process by which a drug molecule leaves a drug product and is subjected to absorption, distribution, metabolism, and excretion (ADME), eventually becoming available for pharmacological action.[1] The mechanism and kinetics of drug release from dosage form devices is a very important discuss in effective drug delivery. The mechanism of drug release will certainly affect the kinetics of drug release.

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Specific kinetics of drug release are desirable and applied in the building of devices for the delivery of medicaments in the management/treatment of certain disease conditions because some treatment regimens may require constant serum level of drug while others may not. For example, zero order release is an ideal delivery condition which is particularly important in antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressants.[2]

Several mathematical models have been used to elucidate the water and drug transport processes and to predict the resulting drug release

kinetics.[3,4] The mathematical description of the entire drug release process is rather difficult, because of the number of physical characteristics that must be taken into consideration. These include the diffusion of water into the matrix, swelling, and drug diffusion out of the device, polymer dissolution, axial and radial transport in a 3-dimensional system, concentration dependent diffusivities of the species, moving boundaries, and changing matrix dimensions, porosity and composition. Each model makes certain assumptions and due to these assumptions, the applicability of the respective models is restricted to certain drug–polymer system.[5,6] worked on complex coacervation as a means of drug delivery;[7] studied the multiparticulate delivery of diclofenac sodium by complex coacervation using a binary mixture of irvingia/gelatin gums. The present study applies the different *in vitro* drug release mathematical kinetic models to analyze and compare the release of diclofenac sodium from complex coacervates of irvingia/gelatin gums and acacia/gelatin gums.

The zero order kinetic describes the systems where the drug release rate is independent of its concentration[8] while the first order kinetic model deals with the release from a delivery system where release rate is concentration dependent[9,10] explained the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets.[11,5] The Korsmeyer-Peppas law enumerated and explained the mechanism of drug release using the *n*-value as explained later in this article.[3,4]

MATERIALS AND METHOD

Materials

Diclofenac sodium powder and ethanol (BDH Chemicals Limited, Poole, England), hydrochloric acid (Philip Harris Limited, England), distilled water (prepared in Madonna University laboratory), acetate and Phosphate buffers (Kern Light Laboratories PVT. LTD. India), gelatin and acacia gum (May and baker, England), *Irvingia gabonesis* gum (Obtained from Madonna University, Rivers state, Nigeria).

Methods

Preparation of Complex Coacervates and Physical Admixtures

The optimum preparation conditions have already been predetermined in our previous work [7]. The coacervates of irvingia/gelatin gums were prepared at ratio strength of 1:2 at a temperature of 25^0C and pH of 4.6 but the coacervates of acacia/gelatin gums were prepared at ratio strength of 2:1 at a temperature of 35 ^{0}C and pH of 4.6. The 25% w/v solution of diclofenac sodium in ethanol was dispersed in the gelatin mucilage by continuous stirring using a magnetic stirrer (Model BL23IA, Bio-Lab Instruments Mfg Co., Mumbai) before adding the gum mucilage and further stirred for 5 minutes using the same magnetic stirrer at a rate of 4000RPM. This was kept in a laboratory fridge (LG. Model No. GC- 379BVA) at 8-15^{o}C for 12 hours.

The physical admixtures of the two formulations were also prepared without temperature and pH considerations though the different ratio strengths were maintained.[6]

Determination of Drug Release Profiles

Hard gelatin capsules containing coacervates equivalent to 500 mg diclofenac sodium were put in an Erweka dissolution unit containing 1000 ml of 0.1 N HCl maintained at 37^{o}C±1. Drug release studies were carried out at a paddle speed of 100rpm. Some 5 ml samples of the dissolution medium were withdrawn at 30, 60, 120, 180, 240, 300 and 360 minutes and the withdrawn volume was always replaced with bland 5 ml 0.1 N HCl maintained at the same temperature.

The samples were spectrophotometrically analyzed at a wavelength of λ_{max}=276nm using a UV spectrophotometer (Pyeunicam, Germany, SP6-450 UV-VIS). The percentage drug released was plotted against time (in minutes).

The same was done for the physical admixtures.[11]

Comparison of Drug Release Profiles

The drug release profiles were compared using a statistical model called the FDA fit factor f_2 (similarity factor).

$$f_2 = 50 \bullet \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

Where n = number of time points.

R_t and T_t = Dissolution data of the two dissolution profiles assessed.[12]

Mathematical Modeling of Drug Release Profiles

The data generated from dissolution studies were subjected to different *in vitro* release mathematical kinetic models whose formulae are represented below.

Zero Order Model

$C = k_0 t$

C = %Released, k_0 = Zero Order rate constant expressed in units of concentration/time (t).[14]

First Order Model

$\text{Log } C_r = \text{Log } C_0 - k_1 t/2.303$

C_r = %Remaining, C_0 = Initial concentration of drug, k_1 = First order constant, t = Time.[7]

Higuchi's Square Root Law Model

$Q = k_H t^{1/2}$

Q = %Released, k_H = Constant reflecting design variables of the system, t = Time.[8]

Hixson-Crowell's Cube root Law Model

$[(100 - f)/100]^{1/3} = 1 - k_{HC} t$

f = %Released, k_{HC} = Rate constant, t = Time.[15]

Determination of drug release mechanism

Korsmeyer-Peppas Model

$M_t/M_\infty = k\, t^n$

$\text{Log } (M_t/M_\infty) = n \text{ Log } t + \text{Log } k$

M_t/M_∞ = Fraction of drug released at time (t), k = Rate constant, '*n*-value' is used to characterise different release mechanisms.[12]

RESULTS AND DISCUSSION

Comparison of the *In Vitro* Drug Release Profiles

Figure-1 below is the in vitro release profiles of diclofenac sodium from complex coacervates and physical admixtures of irvingia/ gelatin gums and acacia / gelatin gums.

Though the physical admixtures of irvingia/gelatin gums and acacia/gelatin gums extended the release of diclofenac sodium up to 240 minutes (4 hours), encapsulation of diclofenac sodium in the coacervates of the aforementioned polymeric gum combinations further sustained the release of diclofenac sodium for more than six hours (6 hours). This shows that the coacervates are good and prospective formulations for sustained drug delivery. The drug release profiles were compared using the FDA fit factor f_2.[13] The release profiles of diclofenac sodium from the physical admixtures were found to be similar (f_2= 60) while those of the complex coacervates were also similar (f_2 = 53).

But, the f_2 values of 34 and 31 for the release profiles from irvingia/gelatin and acacia/gelatin gum complex coacervates when compared with those of their physical admixtures respectively indicate total dissimilarity of the release profiles. The results above further confirm the improvement in the sustained release property of the polymeric gums when used as complex coacervates.[14] Therefore, the similarity in the drug properties of the irvingia/gelatin and acacia/gelatin complex coacervates shows that the drug delivery devices could be substituted for one another in the sustained delivery of diclofenac sodium.[10]

Mathematical Modeling of Drug Release Profiles

Figures 2-9 are plots of different mathematical models used in determining the release kinetics of diclofenac sodium from the physical admixtures and complex coacervates of irvingia/gelatin and acacia/gelatin gums.

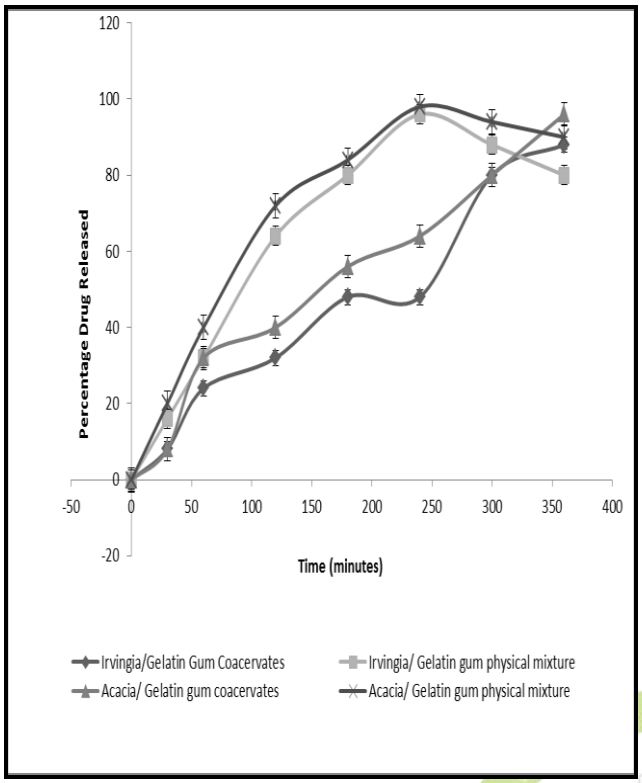

Figure 1: Release profile of diclofenac sodium from coacervates and physical mixtures of irvingia/ Gelatin Gum and Acacia/ Gelatin Gum

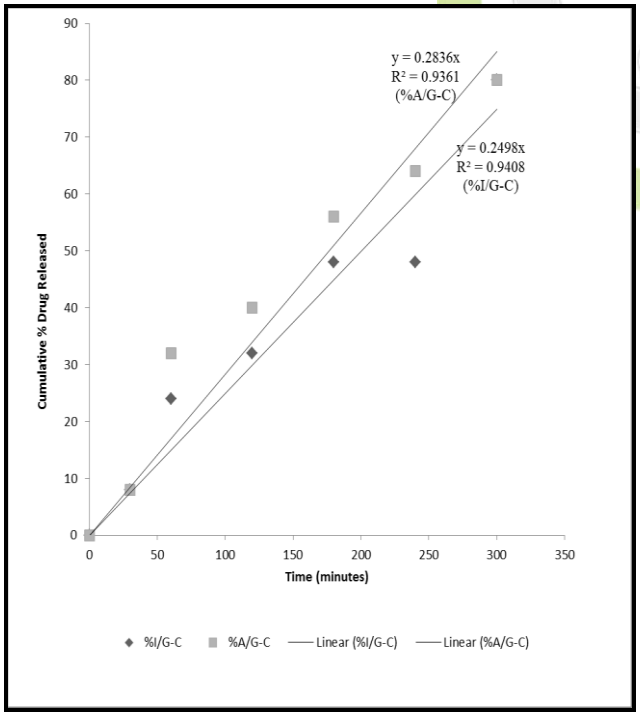

Figure 2: Zero Order Plot of the Release of Diclofenac Sodium from Complex Coacervates of Irvingia/Gelatin Gums (%I/G-C) and Acacia/Gelatin Gums (%A/G-C)

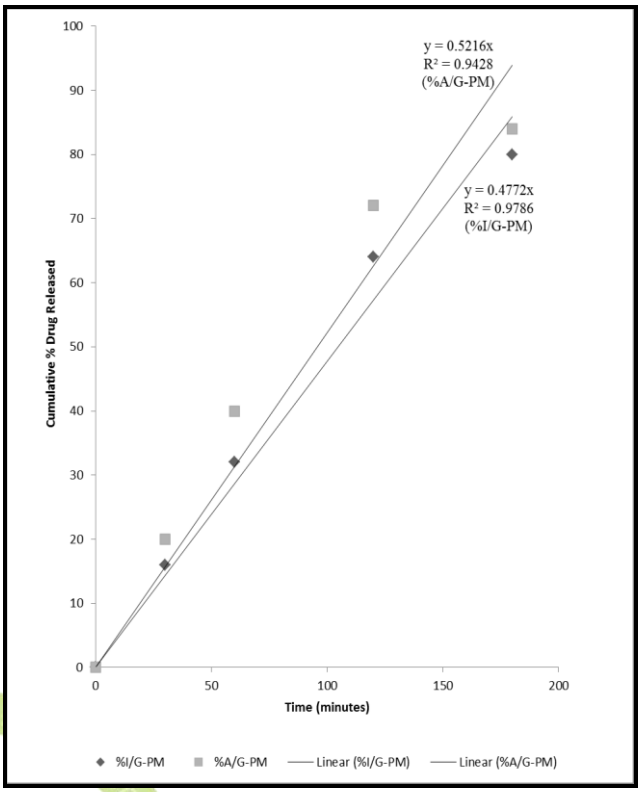

Figure 3: Zero Order Plot of Release of Diclofenac Sodium from Physical Admixtures of Irvingia/Gelatin Gums (%I/G-PM) and Acacia/Gelatin Gums (%A/G-PM)

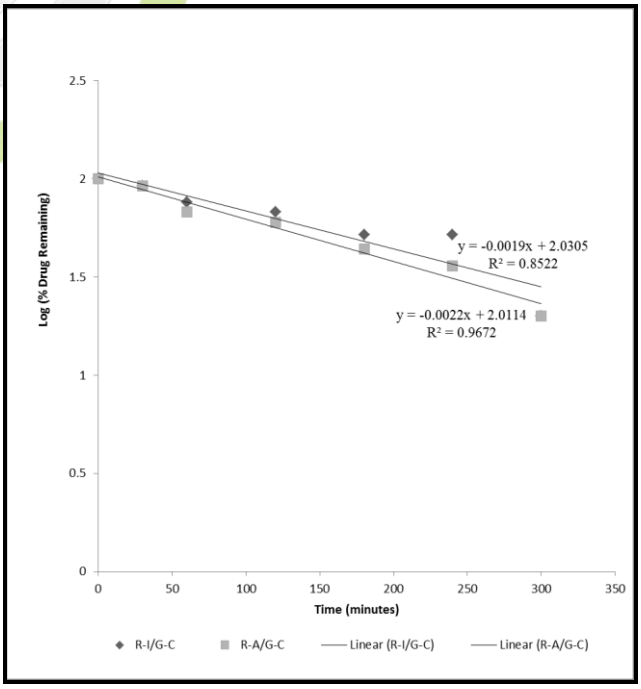

Figure 4: First Order Plot of the Release of Diclofenac Sodium from Complex Coacervates of Irvingia/Gelatin Gums (R-I/G-C) and Acacia/Gelatin Gums (R-A/G-C)

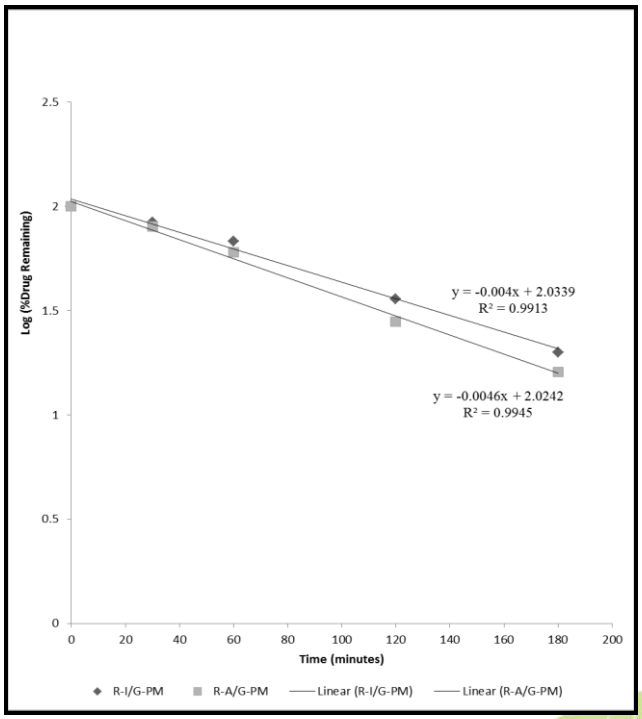

Figure 5: First Order Plot of the Release of Diclofenac Sodium from Physical Admixtures of Irvingia/gelatin Gums (R-I/G-PM) and Acacia/gelatin Gums (R-A/G-PM)

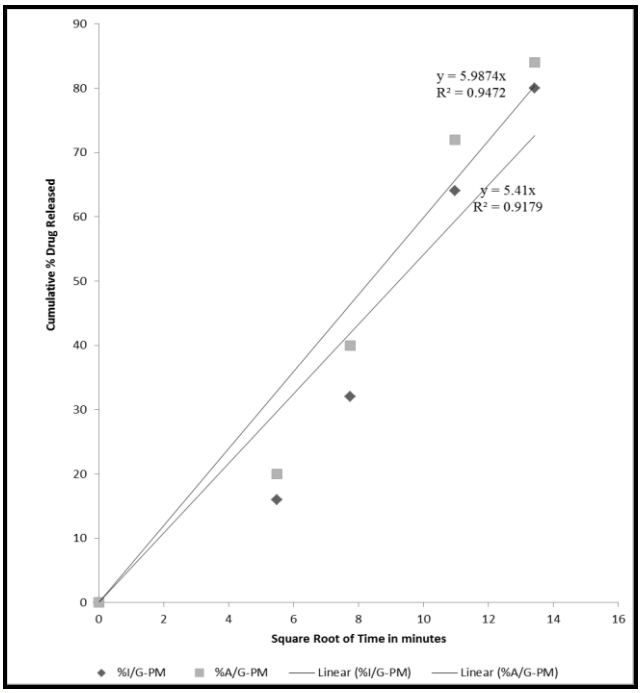

Figure 7: Higuchi's Square Root Plot of the Release of Diclofenac Sodium from PHysical Admixtures of Irvingia/Gelatin Gums (%I/G-PM) and Acacia/Gelatin Gums (%A/G-PM)

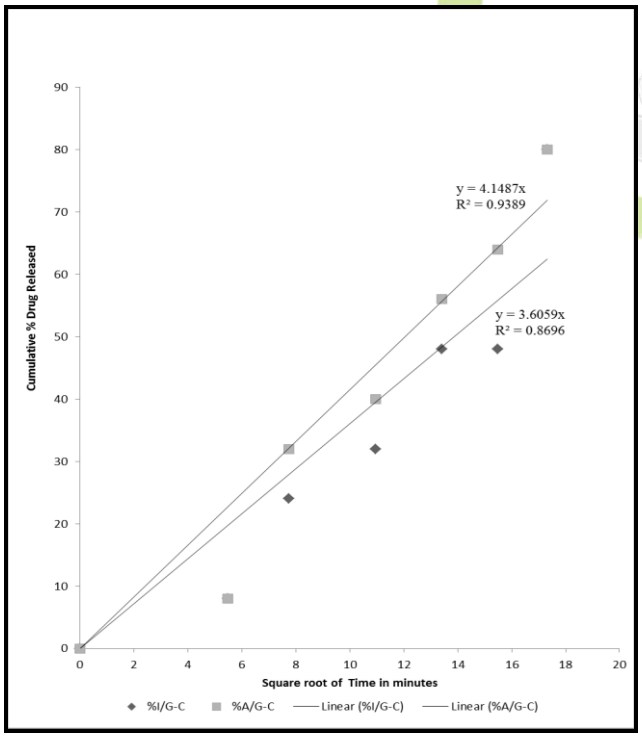

Figure 6: Higuchi's Square Root Plot of the Release of Diclofenac Sodium Complex Coacervates of Irvingia/Gelatin Gums (%I/G-C) and Acacia/Gelatin Gums (%A/G-C)

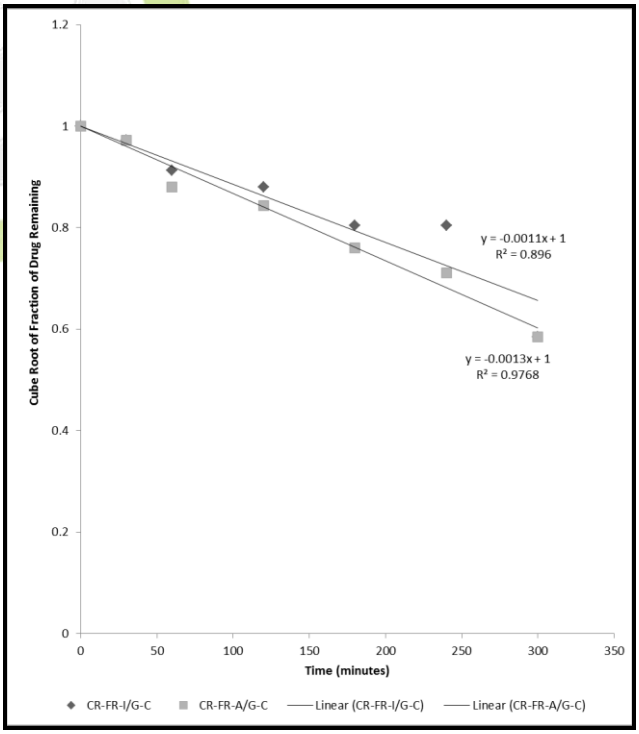

Figure 8: Hixon Crowell's Cube Root Plot of the Release of Diclofenac Sodium from Complex Coacervates of Irvingia/Gelatin Gums (CR-FR-I/G-C) and Acacia/Gelatin Gums (CR-FR-A/G-C)

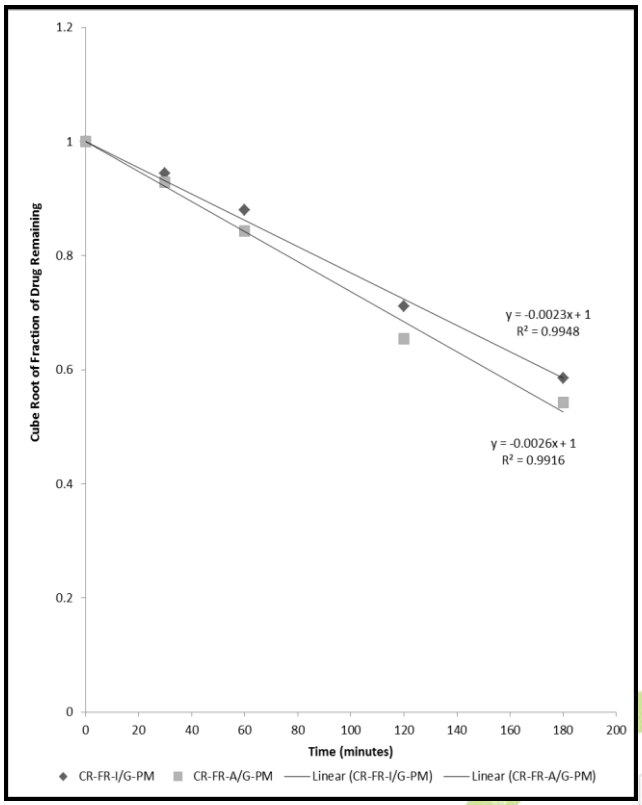

Figure 9: Hixon Crowell's Cube Root Plot of the Release of Diclofenac Sodium from Physical Admixtures of Irvingia/Gelatin Gums (CR-FR-I/G-PM) and Acacia/Gelatin Gums (CR-FR-A/G-PM)

A critical overview of the *in vitro* release kinetics of the dissolution profiles reveals that all the formulations assessed have mixed release kinetics in operation except the complex coacervates of irvingia/gelatin gums where zero order release kinetic dominated with regression value (R^2) of 0.9408. This means that the release of diclofenac sodium from the complex coacervates of irvingia/gelatin gums was not concentration dependent.[6] The K_0-value of the plot of the zero order kinetics (which is a measure of drug release rate) showed a decreased release rate in the transition from physical mixtures to complex coacervates which further confirm the improvement in the sustained release property of the coacervates.[15] Though the drug release from complex coacervates of acacia/gelatin gums and physical admixture of irvingia/gelatin gums were dominated by the Hixson-Crowell cube root kinetic (R^2 = 0.9768 and 0.9948 respectively), the zero order, first order and Higuchi's kinetics (prominent R^2 values > 0.9) were contributing to drug release. That notwithstanding, the drug release from the physical admixture of acacia/gelatin gums was of the first order kinetic (R^2 = 0.9945), though the other aforementioned release kinetics were believed to also be in operation (R^2 > 0.9). The data above show that the release of diclofenac sodium from complex coacervates of acacia/gelatin gums and physical admixtures of irvingia/gelatin gum happened majorly by means of erosion (change in surface area) with some contributions from concentration and diffusion, while drug release from physical admixture of acacia/gelatin gums was majorly concentration dependent with contributions from erosion and diffusion.[5]

Determination of Drug Release Mechanism

Figures 10 and 11 are Korsmeyer-Peppas plots of the release of diclofenac sodium from the physical mixtures and complex coacervates of irvingia/gelatin and acacia/gelatin gums.

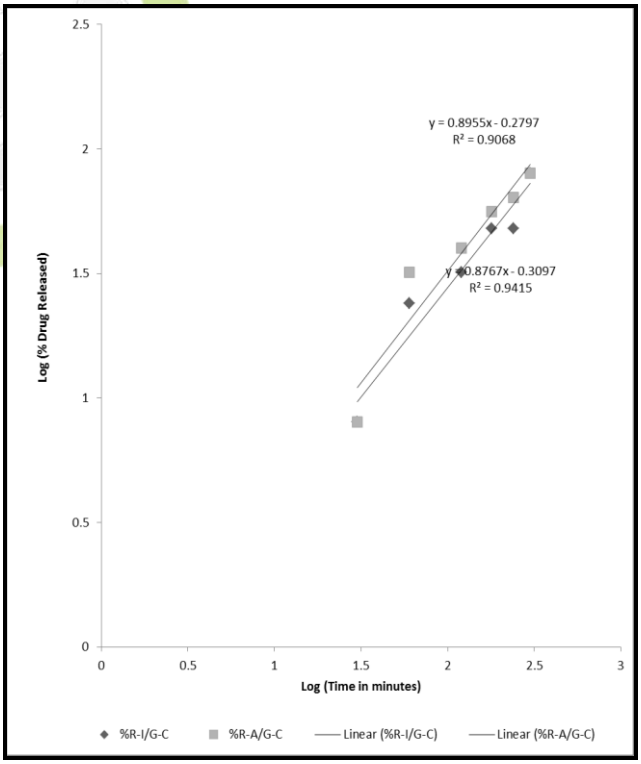

Figure 10: Korsmeyer-Peppas Plot of the Release of Diclofenac Sodium from Complex Coacervates of Irvingia/Gelatin Gums (%R-I/G-C) and Acacia/Gelatin Gums (%R-A/G-C)

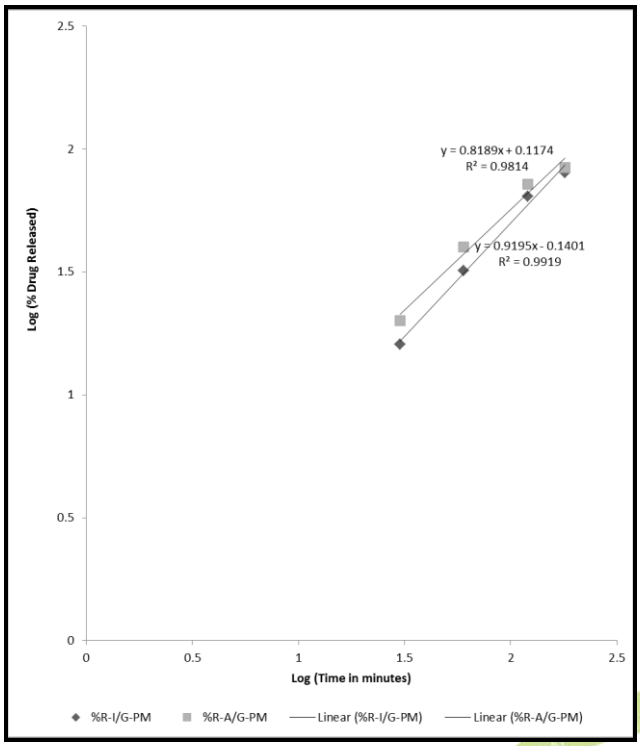

Figure 11: Korsmeyer-Peppas Plot of the Release of Diclofenac Sodium from Physical Admixtures of Irvingia/Gelatin Gums (%R-I/G-PM) and Acacia/Gelatin Gums (%R-A/G-PM)

The first 80% of release data was used in determining the mechanism of release according to Korsmeyer where '***n***' is the release exponent, indicative of mechanism of drug release. The release profiles of all the formulations complied with the Korsmeyer-Peppas plot with regression values (R^2) above 0.9. The mechanism of drug release from the irvingia/gelatin gum coacervates and acacia/gelatin gum physical mixtures was anomalous (non-Fikian) diffusion (*n*-values = 0.8767 and 0.8189 respectively). But, the mechanism of drug release from the acacia/gelatin gum coacervates and irvingia/gelatin gum physical admixtures (*n*-values = 0.8955 and 0.9195 respectively) is super case-II transport.[16] Amazingly, the last two mentioned formulations share the same release kinetics and mechanism but their release profiles were not similar. Notwithstanding the fact that the release profiles of the complex coacervates were dissimilar from those of their physical admixtures, their release kinetic models and mechanisms were also different. Though the coacervate formulations had different release kinetics and mechanisms, the release profile of diclofenac sodium from those delivery devices were similar.

CONCLUSION

The complex coacervates had similar release profiles but their mechanisms of drug release were different and kinetics of drug release followed different mathematical models.

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