Okra (*Hibiscus esculentus*) gum based hydrophilic matrices for controlled drug delivery applications: estimation of percolation threshold

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Abstract:

This study aims to explore the potential of gum extracted from okra fruit (*Hibiscus esculentus*) in developing hydrophilic matrices for controlled drug release applications, including determination of its percolation threshold. Flurbiprofen (poorly soluble), theophylline (sparingly soluble) and metformin (freely soluble) were employed as model drugs and incorporated using direct compression into matrices containing 40% *w/w* of three drugs with different physicochemical properties. Atomic force microscopy was used to study the surface texture properties of developed matrices; the surfaces of the flurbiprofen-based matrices were comparatively rough most likely as a consequence of its poor compactability. Swelling studies found that the swelling rate increased as the concentration of okra gum was increased. However, for all matrices, an increase in the gum concentration resulted in decreased drug release. The estimated percolation threshold of the okra gum calculated was found in the region of ~25% *v/v* plus initial porosity. Knowing the percolation threshold will enable formulators to use the minimal amount of polymer for sustain release matrices thus the controlling costs and maximising the sustainable potential of okra. This study will not only assist researchers in developing effective okra gum-based extended-release matrices but also expected to contribute towards its exploration at an industrial scale.

1. Introduction

Currently, hydrophilic matrix systems are one of the most widely used drug delivery systems used to control drug release rates due to their ability to provide extended-release [1,2]. The intention of most of these systems is to maintain drug levels in the blood within the therapeutic range for a specific duration reducing the need for multiple drug dosing, thus improving patient compliance [3].

Hydrophilic polymers are the major components used in the fabrication of hydrophilic matrix tablets [4] and the most widely used of these is hydroxypropyl methylcellulose (HPMC), a semi-synthetic cellulose derivative [1,5,6]. However, natural polymers are an alternative being relatively abundant, biocompatible, biodegradable and chemically inert, which makes them a good candidate for drug delivery applications [7]. The biopolymer extracted from Okra (*Hibiscus esculentus*) fruit has reported as a natural alternative source to develop hydrophilic matrices [6], having demonstrated the potential of developing extended drug release formulations [8]. Okra (*Abelmoschus esculentus L.*) is a plant which is broadly cultivated in warm, temperate, tropical and subtropical regions around the world with an estimated total annual trade of over $5 billion. The okra pods derived biopolymers are predominately pectins. Pectins are acidic heteropolysaccharides consisting of three segments, namely homogalacturonan (HG), rhamnogalacturonan I (RG-I) and rhamnogalacturonan II (RG-II) regions [9].

Although the formulation development for hydrophilic matrices can be relatively simple, however, drug release mechanisms from these matrices are complicated due to the many different physicochemical processes (swelling, matrix erosion and drug release) which can occur both sequentially and simultaneously [10]. The swelling and the matrix erosion

processes are impacted by many factors which therefore impact the drug release [1,2,11-13]. Drug solubility and polymer concentration must be taken into consideration as, in general, water-soluble drugs undergo diffusion-based release while water-insoluble drugs follow an erosion-based release mechanism [14]. We have previously reported this is the case for okra biopolymer matrix tablets with theophylline releasing more quickly than flurbiprofen, a poorly soluble drug [15]. In such formulations, there needs to be adequate polymer for formation of a uniform gel that acts as a barrier preventing the immediate release of drug; this is known as the critical polymer concentration [11-13]. It is widely accepted that an increase in polymer concentration decreases drug release rates due to more rapid and extensive swelling which restricts the movement of liquid molecules into tablet matrix thus hindering release [16].

There are numerous studies in the literature reported the potential of okra biopolymer in controlling the drug release [8,15,17]. However, there is an important question remain unanswered that at what concentration okra biopolymer start to control drug release as this fundamental information is a key towards its industrial realisation. Classically, percolation theory is employed to estimate the minimum polymer concentration required to attain controlled drug release effect which is a phenomenon based on the formation of the cluster of a site-and/or bond-percolation [18-20]. This Cluster formation is a key fundamental step to achieve control release effect, under concentration will make the formulation vulnerable to disintegration process leading to pharmaceutical formulation failure. However, over concentration will further prolonged the drug stay in the body leading to clinical consequences and accumulation of polymer in the body (Figure 1) [22-26]. Hence, an optimum level of polymer concentration is essential.

In the case of okra biopolymer based hydrophilic matrices, it can be postulated that the okra biopolymer must be present in a sufficient concentration to form a cluster when hydrated, which percolates the whole matrix and results in the formation of a coherent gel layer. Below the percolation threshold, the biopolymer cannot form a percolating cluster and the matrix is less likely to extend the drug release. Hence, the present study aims to explore the potential of okra biopolymer for controlled drug release applications, including an estimation of its percolation threshold. Drugs with different aqueous solubility, flurbiprofen (8.0 mg/L, poorly soluble), theophylline (7.3 g/L, sparingly soluble) and metformin (2.0 g/10 ml, freely soluble), were employed as models [27].

1. Material and methods

2.1. Materials

Fresh okra pods were purchased from a local supermarket (Huddersfield) originating from Pakistan and kept frozen until used. The model drugs, flurbiprofen, theophylline and metformin were purchased from Tokyo Chemical Industry Ltd, UK. The phosphate buffered tablets and hydrochloric acid were purchased from Fisher Scientific Ltd. UK. The tablet filler (micro-crystalline cellulose (MCC)) was purchased from Sigma-Aldrich UK. All the chemicals were of analytical grade.

1.2. Methods

1.2.1 Extraction of okra gum

Extraction and purification of the okra biopolymer was carried out according to the method described by Ghori et al., 2017 [28]. Briefly, the method involved cutting the okra pods longitudinally and removing the seeds, the pods were then blended with phosphate buffer (pH 6.0) and the mixture was heated at 70°C for 1 hour with gentle stirring. Following heating,

the okra-buffer mixture was centrifuged at 4400 rpm for 20 minutes and the supernatant was separated and washed with ethanol. Finally, the extracted biopolymer was filtered and oven dried. Once dried, the extracted polymer was twice re-hydrated and precipitated with ethanol again to produce a bi-purified polymer. Once dried, the biopolymer was ground to powder and stored until further use. Okra biopolymer was extracted in our laboratory and physicochemical characterisation of bi-purified okra biopolymer employed in the current study is reported in [28].

2.2.2 Preparation of powder mixtures

All powder blends containing different okra biopolymer to drug ratios (flurbiprofen, theophylline and metformin, Table 1) were mixed using a Turbula® Shaker-Mixer for 15 min at 50 rpm. To evaluate the content homogeneity, 10 mg samples were taken from each powder mixture and the drug content was determined using UV standard calibration curves at λ_{max} of 247, 272 and 236 nm for flurbiprofen, theophylline and metformin, respectively, and an acceptance limit of 95% – 105% was set.

2.2.3 Characterisation of powder mixtures

Differential scanning calorimetry (DSC) analysis for all the powder samples (plain drug, polymers and their respective powder mixtures) was performed using 5 – 10 mg of powder samples in an atmosphere of flowing nitrogen at 50 mL per minute and temperature program of 10 °C/min from 20 °C to 300 °C.

X-ray diffraction (XRD) analysis of all the powder samples (plain drug, polymers and their respective powder mixtures) was carried out using a D2-Phase X-ray diffractometer (Bruker UK Ltd., UK) equipped with a CuKα radiation source at 30 KV voltage and 10 mA current. Diffraction patterns were obtained in the 2θ range of 5°–100° using 0.02 step sizes.

2.2.4 Preparation of matrix tablets

The powder blends were compacted using a manual hydraulic press equipped with a 13.00 mm die set (Specac® Ltd, UK). Each tablet weight was maintained at 300 ± 2 mg and was compressed at 20 kN with a 30 second dwell time. All matrix tablets were stored in an airtight container over silica gel for 24 hours before further investigations.

2.2.5. Surface characterisation of matrix tablets

Atomic force microscopy, Dimension Icon by Bruker Nano Surfaces, Ltd, UK, was used to analyse the surface texture of okra hydrophilic matrices quantitatively, and the method was adopted as previously described by Ghori et al., 2017 [28]. 3D surface texture parameters were calculated using MATLAB 2017 software (The Math Works, Inc. Natick, MA USA) [29,30].

2.2.5 Swelling studies

Swelling studies were carried out using USP apparatus I, SR II 6-flask (Hanson Research, USA) at 75 rpm at 37 ˚C. The pre-weighed matrix tablet (W_i) of each formulation was immersed in the swelling medium (900 ml, pH 7.2 phosphate buffer). The previously weighed baskets, containing hydrated matrix tablets, were removed, lightly blotted with 125 mm filter paper (Whatman®, UK) to remove excess liquid, reweighed (W_s) and were immediately replaced into the media. The mean weight was determined for each formulation and degree of swelling (S) was calculated using Eq. (1) [6, 15, 28, 29,31]

$$S = \frac{Ws - Wi}{Wi} \times 100 \qquad (1)$$

Where W_i and W_s are the initial dry and swollen weight of the matrix tablet, respectively, at immersion time (t) in the swelling media. The degree of swelling was determined from the mean of three replicates and presented as degree of swelling (S, %) against time (t).

The mathematical model described by Vergnaud 1991 [32] was used to understand the kinetics of the swelling process. The generalized form of the Vergnaud mathematical model is shown in Eq. 2.

$$M = kt^n \qquad (2)$$

Where

M = the amount of liquid transferred.

t = time.

k = swelling constant.

n = swelling exponent.

It has been reported that a value of $n < 0.5$ is indicative of a diffusion-controlled mechanism in which the rate of diffusion is much less that the rate of polymer relaxation in a matrix tablet. However, when $n = 1$, liquid diffuses through the matrix at a constant velocity with an advancing liquid front marking the limit of liquid penetration into the matrix. A value of $0.45 < n < 1$ indicates anomalous behaviour in which diffusion of liquid and polymer relaxation are of the same magnitude [29, 31, 33].

2.2.6 *In vitro* drug release studies

The *in vitro* drug release studies were performed on all okra biopolymer matrices using USP dissolution apparatus II, SR II 6-flask, paddle apparatus (Hanson Research, USA). Phosphate buffer, pH 7.2, was used as a dissolution medium, 900 mL, and was maintained at 37.5 ± 0.5 °C with the paddle speed adjusted to 75 rpm. Aliquots of dissolution medium (5 ml) were withdrawn manually after 5, 10, 15, 20, 25, 30, 60, 120, 240 and 360 min and replaced with an equal amount of fresh dissolution medium to maintain sink conditions. The dissolution samples were then analysed for drug content using UV spectrophotometry. All the dissolution

experiments were carried out in triplicate (n =3) and mean values were then calculated to attain the drug release profiles.

Drug release data was analysed using different mathematical models: zero order, Higuchi, Korsmeyer-Peppas and Peppas-Sahlin mathematical models. The generalised equations of these models are given below Eq. 3-6;

Zero-order equation: $Q = k_0 t$ (3) [34]

Higuchi equation: $Q = k_H t^{1/2}$ (4) [35]

Korsmeyer-Peppas equation: $Q = kt_n$ (5) [36]

Peppas-Sahlin equation: $Q = K_d^m + K_r^{2m}$ (6) [37]

Where Q = the amount of drug remaining at time t, k_0 = zero-order release constant, k_H = Higuchi rate constant, k = Korsmeyer-Peppas kinetic constant, n = exponent indicative of release mechanism, if n = 0.5 it indicates diffusion controlled release mechanism, n = 1.0 indicates erosion controlled mechanism, the values in between, 0.5 < *n* < 1, suggest that two both the processes are involved in drug release mechanism; k_d = diffusion rate constant, k_r = relaxation rate constant and m = Fickian diffusion exponent for controlled release devices of any geometrical shape.

2.2.7 Estimation of percolation threshold

The percolation threshold was calculated by plotting drug release kinetic parameters (Higuchi's slope K_H, normalised Higuchi's slope K_H/% v/v of okra biopolymer, and relaxation constant of Peppas–Sahlin model, K_r) *versus* volumetric fraction of okra biopolymer plus initial porosity. The fundamental equation of percolation theory [19] is as follows;

$$X = S|\rho - \rho_c|^q \quad (7)$$

According to fundamental equation of percolation theory, Eq. 7, if these parameters behave as critical properties, we can expect that

$$X \propto S.(\emptyset - \emptyset_c)^q \qquad (8)$$

Where X is the system property, S is the scaling factor, ρ is the volumetric fraction of the component, ρ_c is the percolation threshold, $(\emptyset - \emptyset_c)$ is the distance to the percolation threshold and q is the critical exponent.

Two linear regression lines were determined for each drug, to estimate the percolation threshold. The point of intersection between two regression lines was taken as an estimation of okra biopolymer percolation threshold.

The initial porosity was calculated using the following Eq. 9:

$$\varepsilon = V_T - \left(\frac{\omega.\%drug}{\rho_d}\right)\left(\frac{\omega.\%\ excipient}{\rho_e}\right) \qquad (9)$$

Where ε is the initial porosity, V_T is the total volume, w is the tablet weight, ρ_d is the drug density and ρ_e is the excipient density.

2. Results and discussion

2.1 Physical characterisation of powder mixtures

A sharp endothermic peak was present for all drugs on DSC thermograms corresponding to their crystalline melt. DSC scans of powder mixtures showed negligible depression in the melting peaks of model drugs indicating that drugs retained their crystallinity and no drug-excipient interaction was evident (Figure 2). The crystallinity of drugs was also confirmed by XRD scans which showed multiple sharp peaks as compare to the okra and MCC (Figure 3). The XRD scan of powder mixture with theophylline showed a sharp characteristic peak at

12.54° whereas multiple depressed peaks were observed for flurbiprofen and metformin based powder blends (Figure 3). Similar to the DSC profiles, XRD scans of powder blends also confirmed that there was no drug-excipient interaction (Figure 4). SEM images (Figure 5, a-h) showed that flurbiprofen has equant shaped crystals, theophylline has elongated crystals with a columnar habit and metformin powder particles are rectangular in shape. Okra gum particles have an irregular shape whereas MCC particles are round in shape. SEM images of powder blends displayed no evidence of agglomeration indicating the development of powder mixtures.

2.2 Surface characterisation of matrices

The surface texture properties of developed tablets was assessed using AFM as surface roughness of directly compressed uncoated matrix tablets plays an important role in dissolution [38]. The results from the 3D surface texture analysis are summarised in Table 2. The surface roughness parameters studied in this analysis related to the amplitude parameters of the surface and included the arithmetical mean height (Sa), root mean square height (Sq), height of the highest peak (Sp), depth of the deepest valley (Sv) and kurtosis (Sku). Results showed a decrease in overall surface roughness (Sa and Sq), maximum peak height (Sp) and maximum valley depth (Sv) as the concentration of okra was increased regardless of the drug used. This was also observed in the 3D AFM surface images of the matrix tablets as displayed in Figures 6-8. These images clearly display an increase in the smoothness of the tablet surface and a reduction in peaks and valleys as the polymer concentration increased in all formulations. This trend may be explained by the fact that there is a direct correlation between particle size and surface roughness [39]. As displayed in Figure 5d and Figure 5e, the particle size of the okra biopolymer is considerably smaller than that of microcrystalline cellulose. Therefore, as the concentration of okra increases and the concentration of

microcrystalline cellulose decreases, the proportion of the matrix tablet composed of smaller particles increases leading to a decrease in surface roughness. However, the surface matrix tablets containing flurbiprofen was rougher than those containing theophylline and metformin (Figure 6-8). This was also evident from all of the amplitude parameters presented in Table 2. This may be explained by the greater irregularity of the particle shape of flurbiprofen crystals (Figure 5a) compared with theophylline (Figure 5b) and metformin HCl which are more regular (Figure 5c). Furthermore, the flurbiprofen tablets displayed a spiked distribution (Sku > 3) in peak height distribution indicating the presence of inordinately high peaks and deep valleys at all concentrations of okra apart from 40% w/w [30]. In comparison, the matrix tablets containing theophylline and metformin HCl presented a spiked distribution in peak height at an okra concentration of 10% w/w, whereas at higher concentrations, the peak height distribution was skewed above the mean plane (Sku < 3). Overall, it can be concluded, regardless of drug type, the okra biopolymer concentration above 20% *v/v* produced matrices with smooth surfaces.

2.3 Swelling studies

It is apparent from Figure 9 that all okra biopolymer matrices, regardless of type of drug used, swell and gain weight over time. The physical and visual assessment confirmed the development of a so-called gel on the surface of the matrix tablets. All the matrices were slippery to touch and initially underwent swelling, although this stopped or tablets were subject to erosion at later times. The overall swelling behaviour of okra biopolymer matrices in current study may be due the osmotic stress, engendered due to liquid imbibition, exerted at the moving front located between dry glassy core and the outer-most surface gel layer. This whole phenomenon is mainly controlled by two processes, namely solvent diffusion and chain disentanglement. On contact with the liquid, the liquid will imbibe into the okra and

due to plasticisation of the biopolymer chains by the solvent, a gel-like swollen layer is formed on the surface of the matrix tablet formed [28].

It is apparent that the drug solubility and concentration of okra biopolymer in a matrix tablet both impact liquid uptake behaviour, Figure 9. The results showed that the extent of swelling (%) was increased as the content of okra biopolymer increased from 10 to 40 % *w/w* in the matrices. However, the matrices containing poorly soluble drug (flurbiprofen) swell less than those containing more soluble drugs.

To understand the swelling kinetics of the matrices the data were analysed using Vergnaud's liquid uptake mathematical model [32]. The swelling kinetics parameters are summarised in Table 3 providing information liquid diffusivity and polymer relaxation as described by various investigators [24,31,33]. Data were well described by this model with correlation coefficients, R^2, ranging from 0.960 - 0.999. The swelling rate (K_w) increased as the okra biopolymer concentration increased and drug solubility increased for all formulations. All the matrices, regardless of drug, displayed anomalous behaviour (i.e. the rate of water diffusion and polymer relaxation are of similar magnitude). However, when the okra biopolymer content increased from 10 to 40 % *w/w* the swelling behaviour tended towards a more diffusion controlled mechanism. This is likely due to ionisation of the carboxyl group within the okra biopolymer which increases the permeability of water molecules in the polymer network and the development of ionic bonds incorporating water molecules [40,41]. Hence, higher polymer content will lead to increased ionic bonding and capacity for water retention leading to diffusion dominant swelling.

2.4 Drug release kinetics studies

The *in vitro* drug release profiles of flurbiprofen, theophylline and metformin from the tablets are shown in Figure 10. It was seen that okra concentration played an important role in extending the drug release from matrix tablets. An inverse relation was seen between okra concentration and drug release, i.e. for all matrices, an increase in okra concentration resulted in decreased drug release, irrespective of drug solubility. The formation of a gel layer around the matrix restricts the movement of liquid across the matrix. Consequently, it impedes drug movement leading to decreased drug release. Furthermore, the relative drug solubility also had an effect on drug release, with release rate increasing with increasing solubility (i.e. flurbiprofen < theophylline < metformin). Highly-soluble drugs act as pore formers leading to the formation of micro-cavities, rendering the gel structure more porous and weaker, hence leading to increased drug release rates. Poorly soluble drugs, however, are released predominantly by erosion of the gel matrix, as the drug particles translocate and their presence compromises the structural integrity of the gel layer present on the surface of the matrix tablet, leading to drug release through matrix erosion.

The dissolution data exhibited a good fit to all models indicating a linear relationship with correlation-coefficient (R^2) values between 0.95-0.99 for zero order, 0.96-0.99 for Higuchi and 0.99 for Korsmeyer-Peppas and Peppas-Sahlin's models (Table 4). Overall, drug release rates decreased with increasing okra concentration. Theophylline and metformin tablets had a good fit to the Higuchi equation indicating a release mechanism mainly controlled by diffusion, however, according to Korsmeyer-Peppas release kinetics criteria for swellable cylindrical drug delivery systems, all okra tablet matrices showed an anomalous transport or non-Fickian release mechanism. Moreover, as the okra biopolymer concentration increased,

the *n* value fell from 0.82 to 0.75, 0.66 to 0.57 and 0.60 to 0.56 for flurbiprofen, theophylline and metformin, respectively (Table 4). It can be deduced that a combination of release mechanisms, diffusion and erosion, were involved in drug release from okra matrix tablets, however, erosion dominated for flurbiprofen and diffusion for theophylline and metformin. The Peppas-Sahlin model also confirmed that a combination of drug release mechanisms (diffusion and erosion) were involved in drug release from okra biopolymer matrices.

2.5 Estimation of okra biopolymer percolation threshold

The values of percolation threshold were estimated by plotting the kinetic parameters Higuchi rate constant (K_H), relaxation rate constant (K_r), normalised Higuchi and relaxation rate constant versus % *v/v* of okra biopolymer plus initial porosity. Volume fractions were used in the calculations as the ability of particles to contact with other particles to form a continuous cluster depends on the volume of polymer within the matrix and not on the weight of the polymer [1,2]. The results for estimated percolation threshold of okra biopolymer with flurbiprofen, theophylline and metformin are shown in Figures 11-13. It can be observed that two linear regressions were plotted, for each drug, to estimate the percolation threshold as the intercept point between regression lines. The percolation threshold (intercept value) was found to be between 20% and 26% v/v of okra biopolymer plus initial porosity [24, 42].

Drug solubility had an impact on the critical concentration threshold, with increased aqueous solubility of drug, the percolation threshold of okra biopolymer was also increased. The calculated percolation threshold of okra biopolymer for matrices containing flurbiprofen, theophylline and metformin is 20.27 - 20.84%, 23.19 - 23.65% and 25.24 -26.14%, respectively (Table 5). This is due to the fact that water soluble drugs tend to have faster release as compared to poorly soluble drugs and the amount of polymer also plays a decisive role in

controlling the release of drugs as shown by previous studies [43,44]. Contrary to this, it has been reported that drug solubility had no significant impact on the percolation threshold of HPMC, a hydrophilic polymer of semi-synthetic origin [42].

Moreover, no substantial differences were noticed in percolation threshold and intercept value calculated for flurbiprofen and theophylline matrices. However, metformin showed a slight increase in percolation threshold when calculated by two different kinetic parameters, Higuchi rate constant and relaxation rate constant are 25.24 and 26.03 % *v/v* plus initial porosity, respectively (Table 5). In accordance with the percolation theory the critical points for flurbiprofen, theophylline and metformin formulations are exists in the region of 25% *v/v*. This can be useful for sustainable production of formulations needing the minimum amount of biopolymer and may be calculated for all biopolymers to inform design and development.

3. Conclusions

The present study has demonstrated the potential of okra biopolymer in developing extended drug release matrices with successful estimation of percolation threshold. It can be concluded from the findings that okra biopolymer particles develop a percolating cluster as the initial porosity contributed to the swelling process responsible for controlling the release of drugs. It can be concluded that as the concentration of okra biopolymer increases it lead to smooth surface tablets. The relationship between the percolating cluster components is linear, consequently, valid for the elucidating percolation threshold which revealed the critical points controlling drug release exists in the region of 25% *v/v*. This may be beneficial for sustainable production of hydrophilic matrix tablet formulations needing minimum amount of okra biopolymer. Moreover, these findings may be useful in controlling costs and maximising the sustainable potential of okra biopolymer especially in developing countries where

pharmaceutical manufacturing sector depends on petrochemicals as majority of raw materials are being imported. Overall, it can be concluded that the novel findings of okra biopolymer percolation threshold in developing hydrophilic matrices for controlled release applications contribute to improve their design, robustness, functionality and manufacturing. Hence, this study will not only assist researchers in developing effective okra biopolymer-based extended-release matrices but also expected to contribute towards its exploration at an industrial scale.

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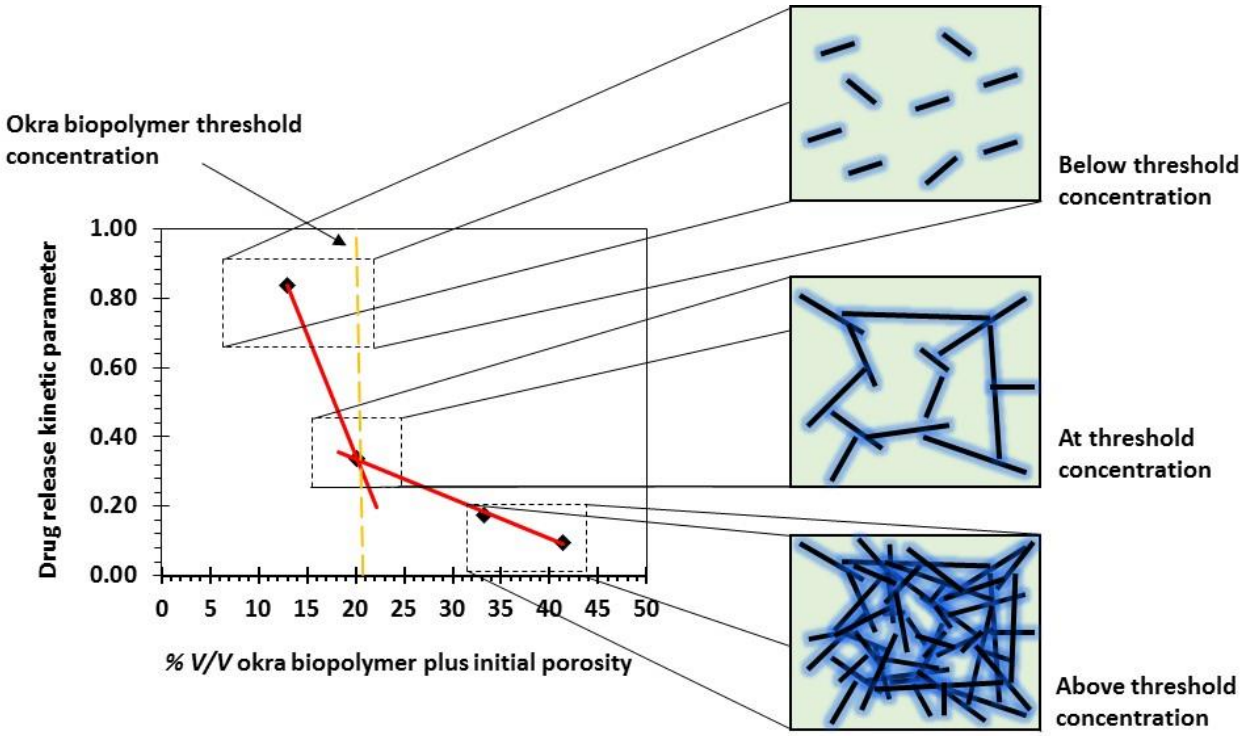

Figure 1: Schematic illustration showcasing the percolation threshold importance in control release formulations.

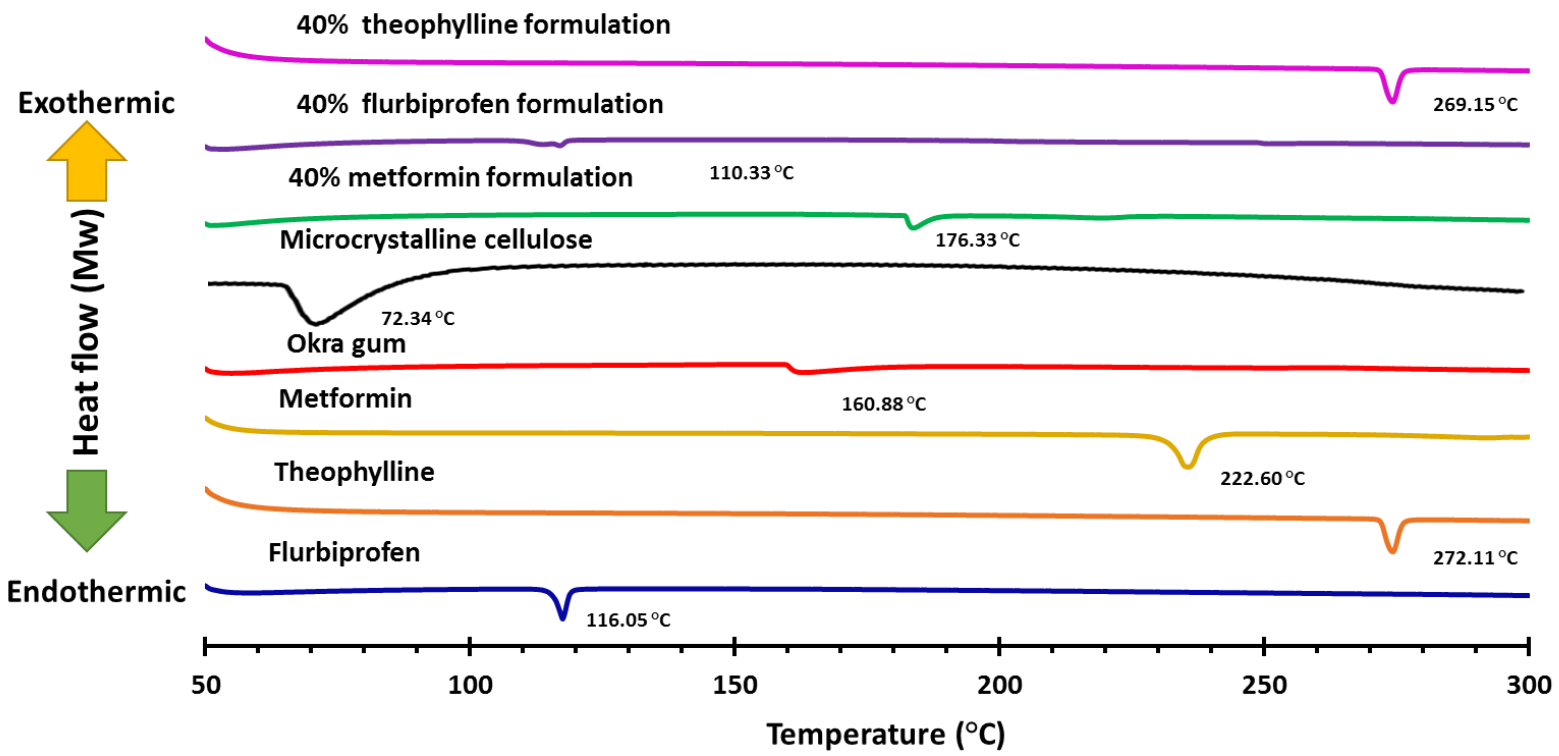

Figure 2, DSC thermograms of drugs (flurbiprofen, theophylline and metformin), okra gum, microcrystalline cellulose and 40% wt. powder mixtures

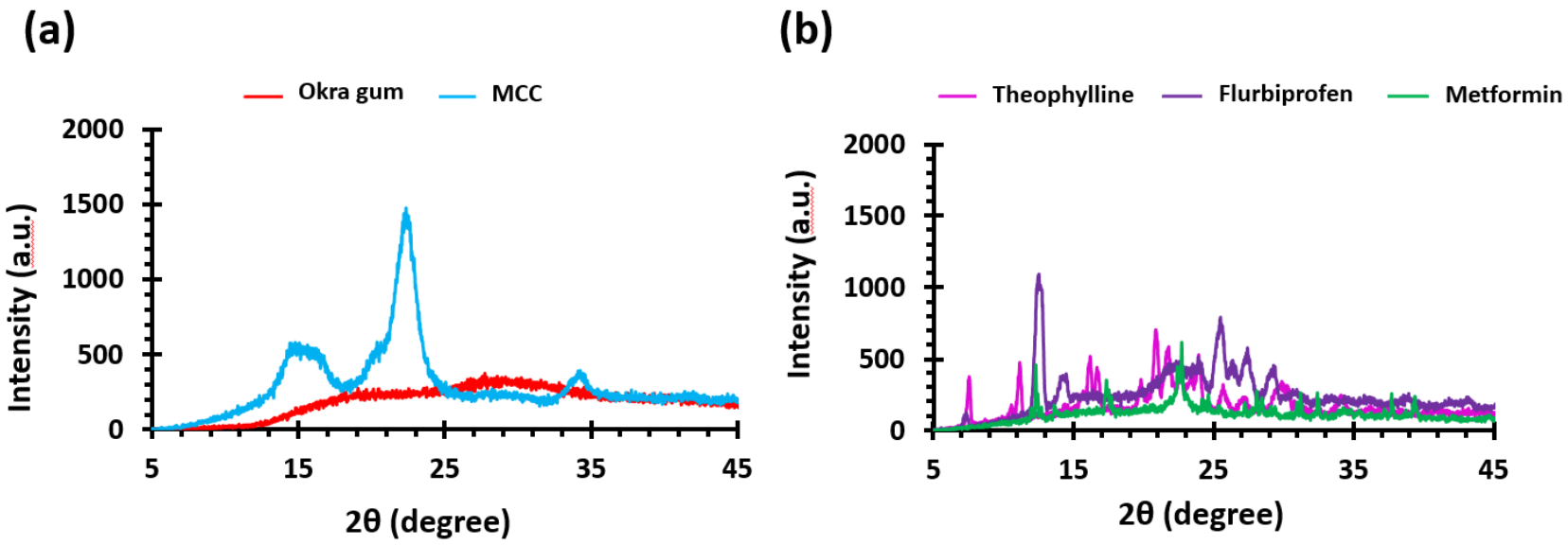

Figure 3, XRD patterns of (a) excipients and (b) drugs used in this study

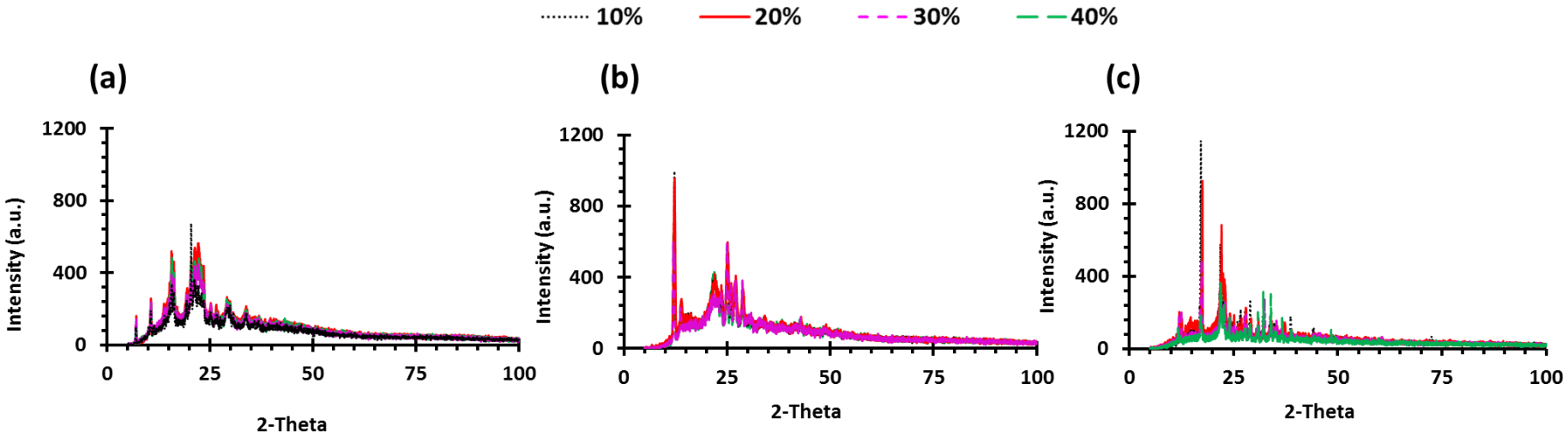

Figure 4, XRD patterns of powder mixtures (10, 20, 30 and 40% w/w okra gum concentration), (a) flurbiprofen (b) theophylline (c) and metformin

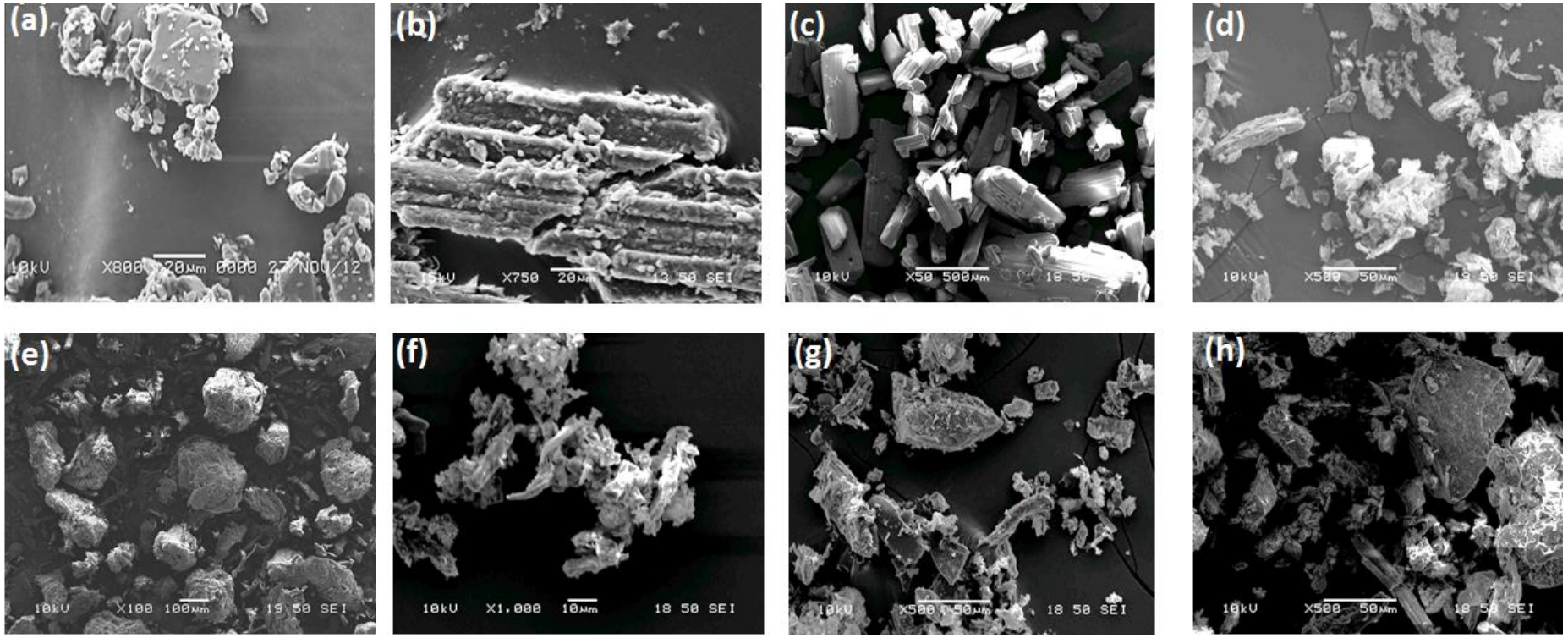

Figure 5, SEM micrographs of (a) flurbiprofen (b) theophylline (c) metformin (d) okra gum (e) microcrystalline cellulose, (f) 40% wt. powder mixture of okra biopolymer with fluriprofen, (g) 40% wt. powder mixture of okra biopolymer with theophylline and (h) 40% wt. powder mixture of okra biopolymer with metformin.

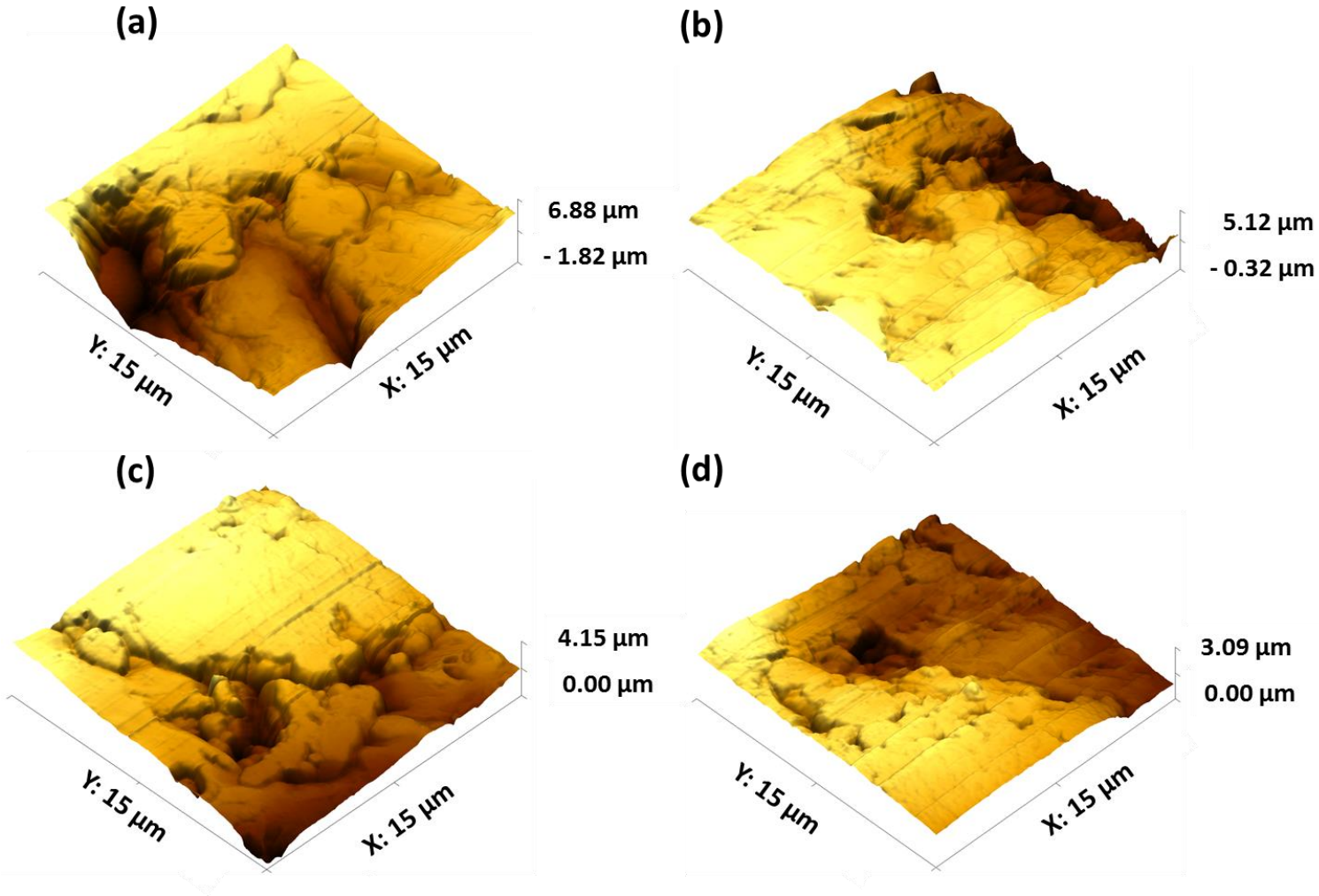

Figure 6, 3D AFM surface images of flurbiprofen based matrix tablets containing (a) 10, (b) 20, (c) 30 and (d) 40 % *w/w* okra gum.

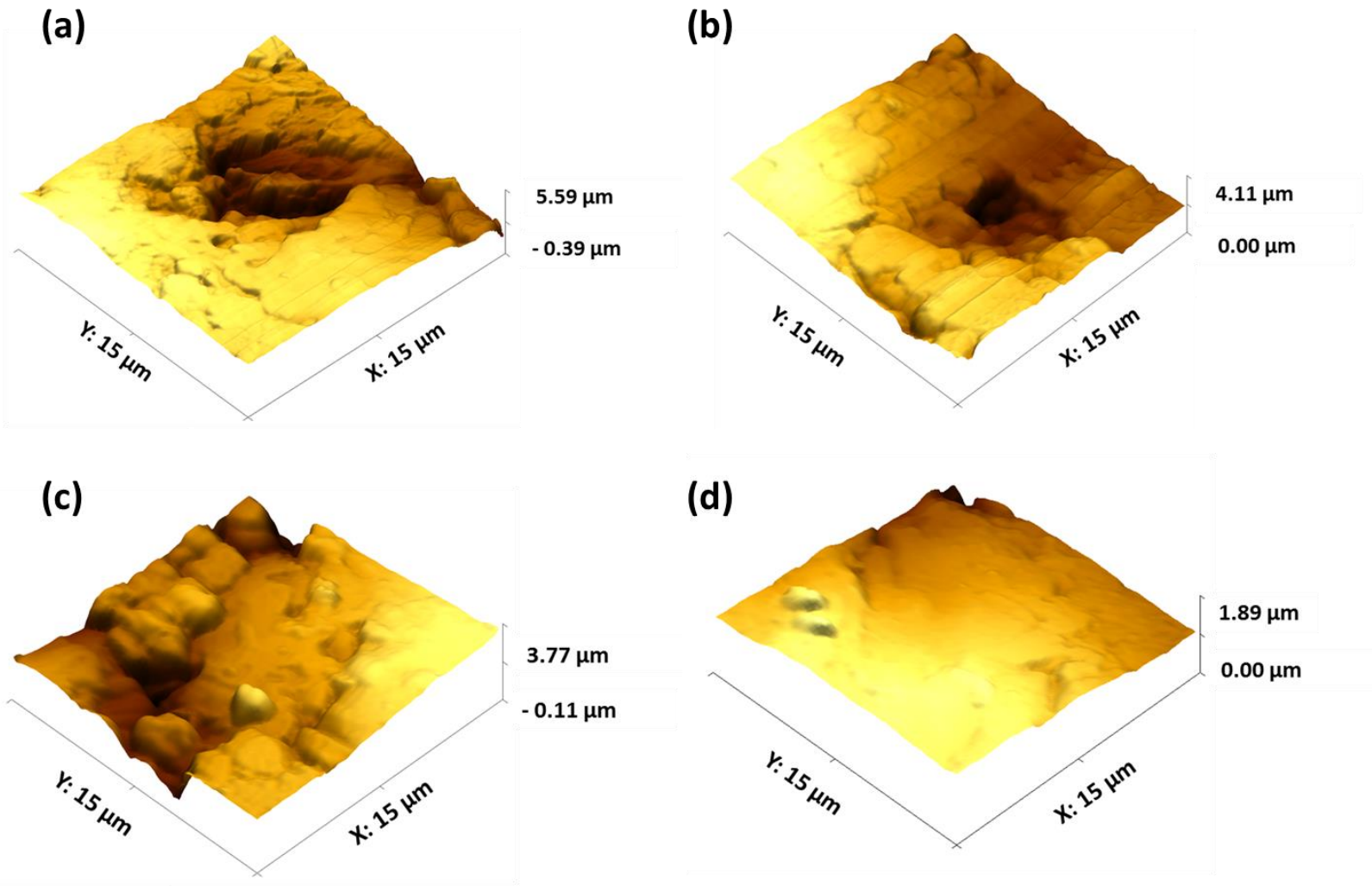

Figure 7, 3D AFM surface images of theophylline based matrix tablets containing (a) 10, (b) 20, (c) 30 and (d) 40 % *w/w* okra gum.

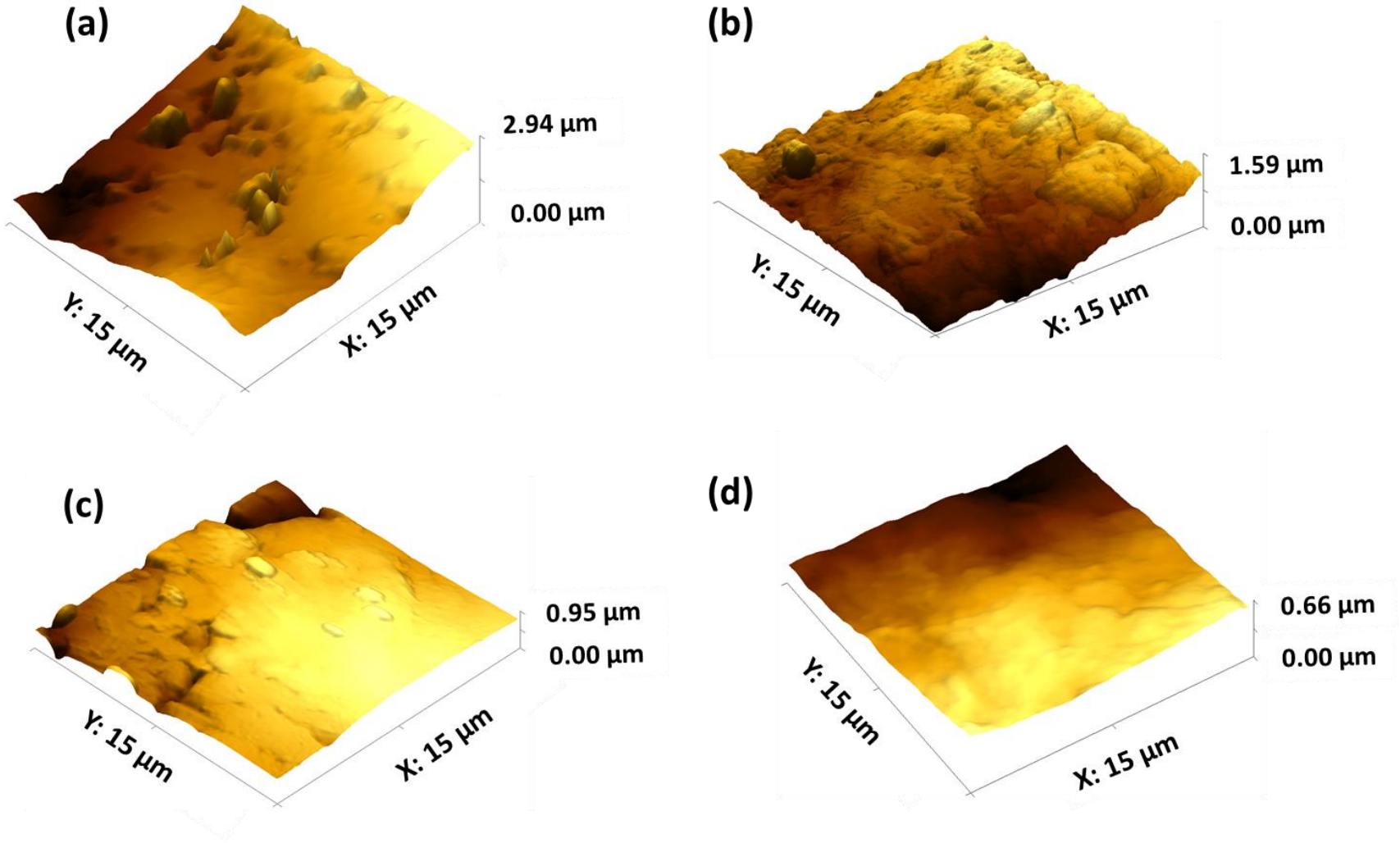

Figure 8, 3D AFM surface images of metformin HCl based matrix tablets containing (a) 10, (b) 20, (c) 30 and (d) 40 % *w/w* okra gum.

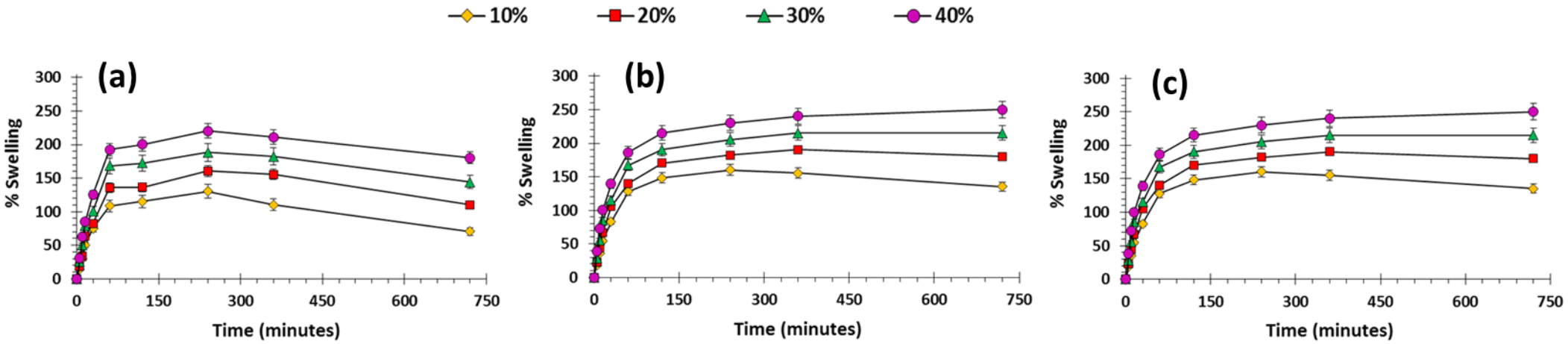

Figure 9, Swelling profiles, with respect to time, of okra gum matrix tablets containing (a) flurbiprofen, (b) theophylline and (c) metformin as a model drug.

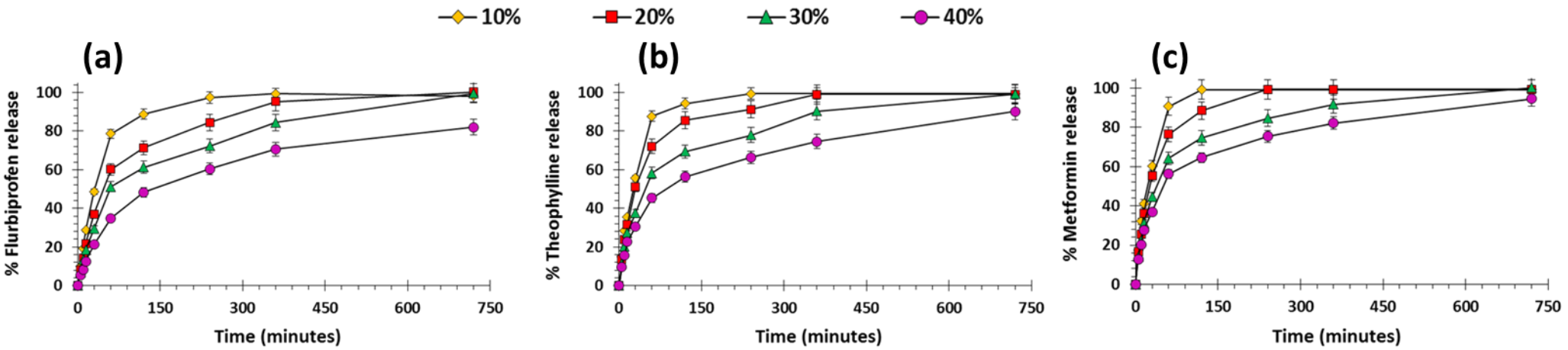

Figure 10, Drug release profiles, with respect to time, of okra gum matrix tablets containing (a) flurbiprofen, (b) theophylline and (c) metformin as a model drug.

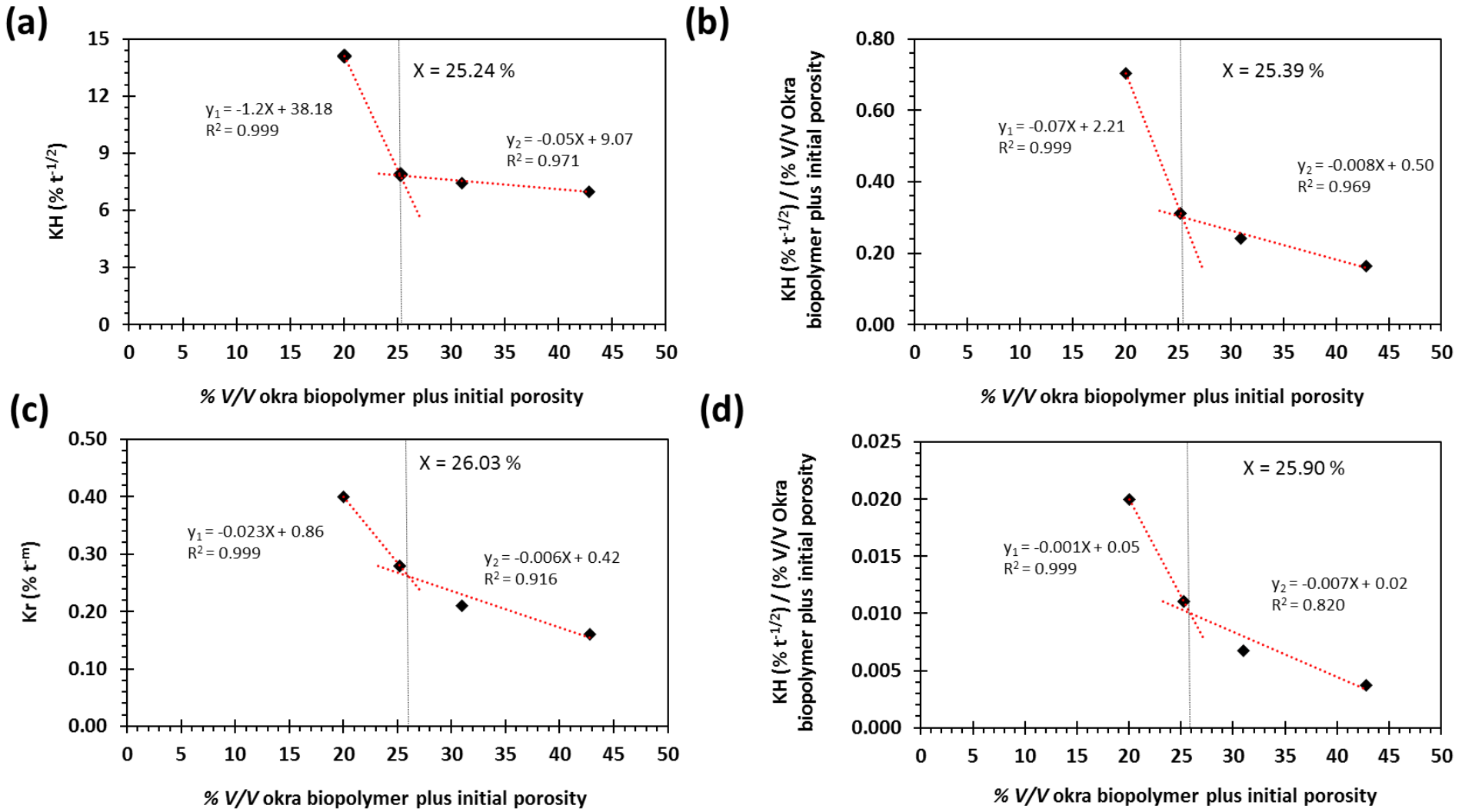

Figure 11, Percolation threshold estimation of metformin: okra gum matrices.

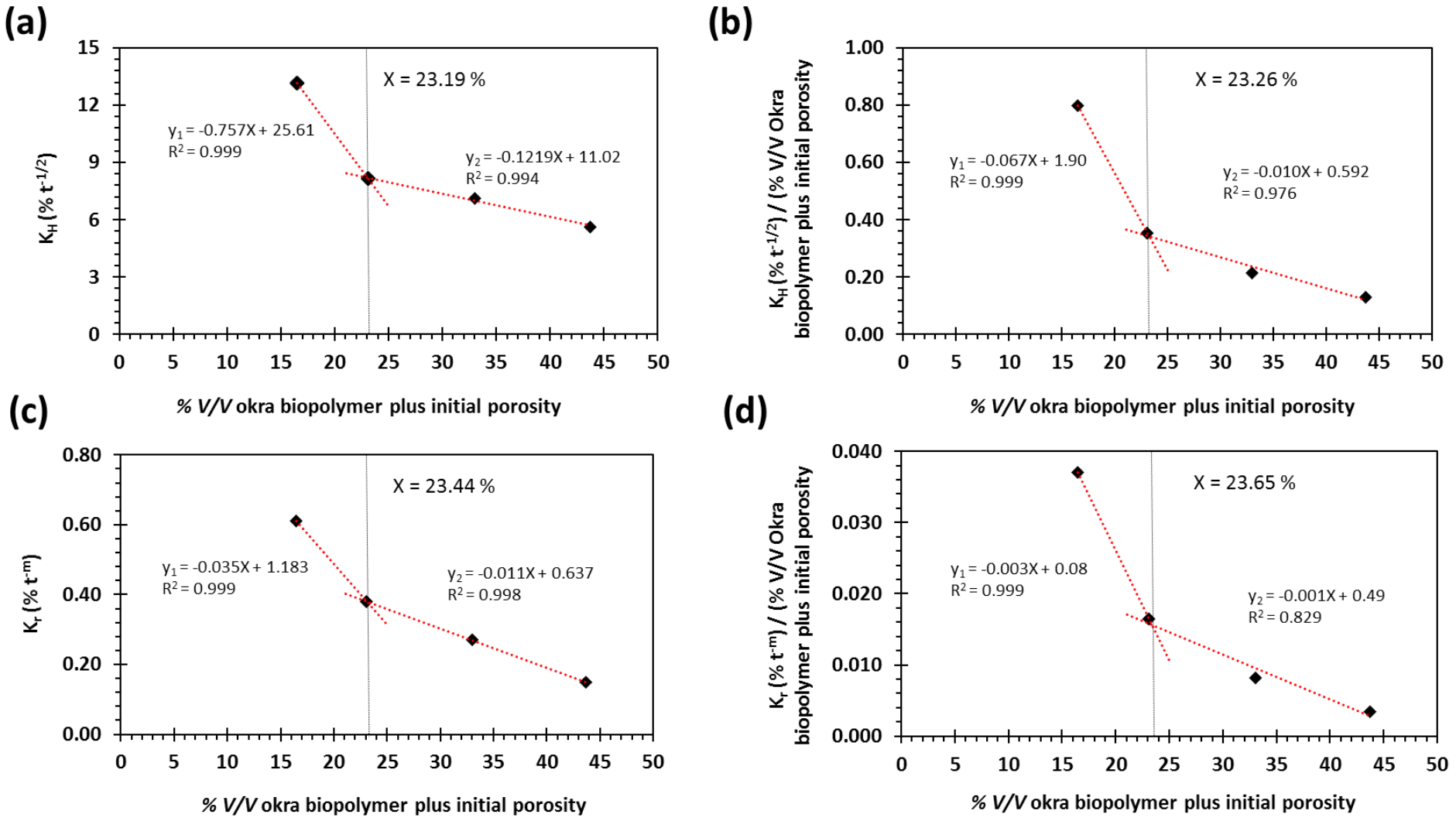

Figure 12, Percolation threshold estimation of theophylline: okra gum matrices.

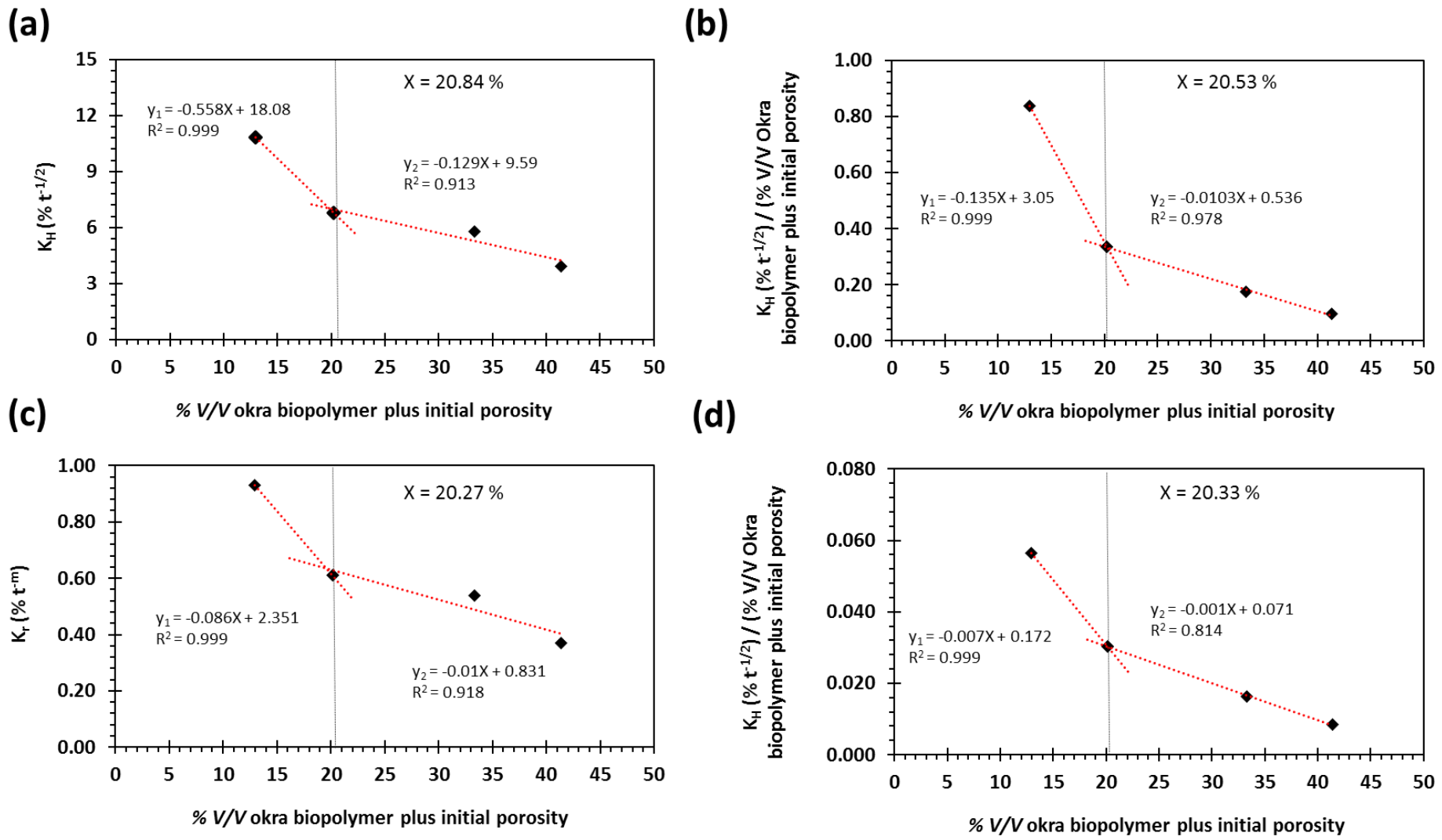

Figure 13, Percolation threshold estimation of flurbiprofen: okra gum matrices.

Table 1: Formulation scheme and polymer volume plus porosity of okra biopolymer matrix tablets

Drug	Drug (% *w/w*)	Okra biopolymer (% *w/w*)	MCC *(% w/w)*	% v/v Okra biopolymer plus initial porosity
Flurbiprofen	40	10	50	12.96 (0.5)
	40	20	40	20.19 (1.1)
	40	30	30	33.30 (1.5)
	40	40	20	41.37 (1.3)
Theophylline	40	10	50	16.48 (1.8)
	40	20	40	23.09 (2.3)
	40	30	30	33.04 (2.1)
	40	40	20	43.71 (3.1)
Metformin	40	10	50	14.14 (1.5)
	40	20	40	23.76 (1.6)
	40	30	30	31.57 (1.3)
	40	40	20	43.19 (1.1)

Table 2: 3D surface texture parameters of okra biopolymer matrix tablets

Surface texture parameter	Okra biopolymer (% *w/w*)											
	Flurbiprofen				Theophylline				Metformin HCl			
	10	*20*	*30*	*40*	*10*	*20*	*30*	*40*	*10*	*20*	*30*	*40*
Sa (µm)	6.2 (0.61)	4.6 (0.13)	3.8 (0.10)	3.4 (0.11)	3.7 (0.10)	2.9 (0.09)	2.6 (0.17)	1.9 (0.12)	3.1 (0.08)	2.5 (0.04)	2.0 (0.11)	1.5 (0.11)
Sq (µm)	7.2 (0.88)	5.1 (0.21)	4.6 (0.19)	3.9 (0.13)	4.6 (0.23)	3.9 (0.16)	3.1 (0.13)	2.1 (0.10)	3.9 (0.13)	3.1 (0.11)	2.7 (0.05)	2.12 (0.16)
Sp (µm)	110.2 (10.1)	90.1 (6.5)	77.5 (4.6)	50.2 (3.6)	77.6 (4.1)	59.3 (3.6)	51.2 (2.1)	46.3 (4.9)	66.2 (5.6)	54.2 (6.1)	44.6 (3.8)	39.5 (5.09)
Sv (µm)	89.6 (4.8)	80.9 (3.2)	70.5 (3.6)	61.5 (5.9)	77.6 (1.9)	69.6 (2.1)	60.9(2.3)	58.2 (2.6)	74.3 (3.6)	62.3 (5.1)	50.5 (3.9)	41.9 (2.3)
Sku (µm)	4.1 (0.10)	3.9 (0.21)	3.7 (0.11)	2.9 (0.12)	3.3 (0.01)	2.9 (0.13)	2.6 (0.21)	2.1 (0.01)	3.1 (0.12)	2.5 (0.30)	1.9 (0.11)	1.7 (0.21

Table 3: Swelling kinetics parameters of okra biopolymer based hydrophilic matrices.

Drug	Okra biopolymer (% *w/w*)	Swelling kinetics parameters		
		n	***K_w***	***R^2***
Flurbiprofen	10	0.82	3.88	0.97
	20	0.79	5.31	0.96
	30	0.74	8.38	0.97
	40	0.72	9.97	0.98
Theophylline	10	0.78	5.34	0.99
	20	0.74	6.74	0.97
	30	0.70	9.52	0.96
	40	0.62	14.63	0.97
Metformin	10	0.75	6.58	0.97
	20	0.72	8.39	0.96
	30	0.65	12.46	0.98
	40	0.60	17.34	0.97

Table 4: Drug release kinetic parameters of okra biopolymer matrix tablets

Drug	Okra biopolymer (% *w/w*)	Zero-order equation		Higuchi equation		Korsmeyer equation			Peppas-Sahlin equation		
		K_0 (%t^{-1})	R^2	K_H (% $t^{-1/2}$)	R^2	K (% t^n)	n	R^2	K_r (% t^{-m})	K_d (% t^{-2-m})	R^2
Flurbiprofen	10	1.42	0.986	10.84	0.982	3.53	0.82	0.991	0.93	3.98	0.991
	20	1.07	0.991	6.80	0.974	2.66	0.80	0.992	0.61	2.84	0.999
	30	0.91	0.990	5.78	0.961	2.27	0.78	0.999	0.54	2.50	0.999
	40	0.63	0.992	3.95	0.975	1.58	0.75	0.993	0.37	1.74	0.999
Theophylline	10	1.61	0.987	13.15	0.981	5.87	0.66	0.999	0.61	6.65	0.994
	20	1.37	0.965	8.15	0.990	5.86	0.62	0.990	0.38	6.60	0.990
	30	1.09	0.962	7.10	0.998	4.95	0.60	0.999	0.27	5.47	0.992
	40	0.86	0.961	5.64	0.997	4.36	0.57	0.996	0.15	4.74	0.999
Metformin	10	1.70	0.972	14.12	0.995	7.79	0.60	0.998	0.40	8.62	0.996
	20	1.47	0.960	7.88	0.992	7.16	0.58	0.995	0.28	7.89	0.995
	30	1.22	0.958	7.45	0.984	6.28	0.57	0.991	0.21	6.81	0.999
	40	1.06	0.961	6.98	0.990	5.63	0.56	0.999	0.16	6.01	0.998

Table 4: The values of percolation thresholds of okra biopolymer matrix tablets

Drug	Kinetic parameters	Equations	R^2	Intercept
Flurbiprofen	$K_H(\%t^{-1/2})$	$Y_1 = -0.558x + 18.08$ $Y_2 = -0.129x + 9.59$	0.999 0.913	X = 20.84
	$K_H(\%t^{-1/2})$/ %v/v okra biopolymer plus initial porosity	$Y_1 = -0.135x + 3.05$ $Y_2 = -0.0103x + 0.536$	0.999 0.978	X= 20.53
	$K_r(\%t^{-m})$	$Y_1 = -0.086x + 2.351$ $Y_2 = -0.01x + 0.831$	0.999 0.918	X = 20.27
	$K_r(\%t^{-m})$/ %v/v okra biopolymer plus initial porosity	$Y_1 = -0.007x + 0.172$ $Y_2 = -00.001x + 0.071$	0.999 0.814	X = 20.33
Theophylline	$K_H(\%t^{-1/2})$	$Y_1 = -0.757x + 25.61$ $Y_2 = -0.1219x + 11.02$	0.999 0.994	X = 23.19
	$K_H(\%t^{-1/2})$/ %v/v okra biopolymer plus initial porosity	$Y_1 = -0.067x + 1.90$ $Y_2 = -0.010x + 0.592$	0.999 0.976	X = 23.26
	$K_r(\%t^{-m})$	$Y_1 = -0.035x + 1.183$ $Y_2 = -0.011x + 0.637$	0.999 0.998	X = 23.44
	$K_r(\%t^{-m})$/ %v/v okra biopolymer plus initial porosity	$Y_1 = -0.003x + 0.08$ $Y_2 = -0.001x + 0.49$	0.999 0.829	X= 23.65
Metformin	$K_H(\%t^{-1/2})$	$Y_1 = -1.2x + 38.18$ $Y_2 = -0.05x + 9.07$	0.999 0.971	X= 25.24
	$K_H(\%t^{-1/2})$/ %v/v okra biopolymer plus initial porosity	$Y_1 = -0.07x + 2.21$ $Y_2 = -0.008x + 0.50$	0.999 0.969	X =25.39
	$K_r(\%t^{-m})$	$Y_1 = -0.023x + 0.86$ $Y_2 = -0.006x + 0.42$	0.999 0.916	X = 26.03
	$K_r(\%t^{-m})$/ %v/v okra biopolymer plus initial porosity	$Y_1 = -0.001x + 0.05$ $Y_2 = -0.007x + 0.02$	0.999 0.820	X =26.14