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Modifying the three-dimensional network of polyamide 6,10 for designing a novel drug delivery system

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CHAPTER TWO

INVESTIGATING THE INFLUENCE OF STOICHIOMETRIC AND VOLUMETRIC RATIO VARIATIONS (PARTIAL MODIFICATION) ON THE PHYSICOCHEMICAL AND PHYSICOMECHANICAL PROPERTIES OF POLYAMIDE 6,10 GUIDED THROUGH A SCREENING EXPERIMENTAL DESIGN

2.1. INTRODUCTION

The recent resurgence in advanced developments with drug delivery systems intended for applications through various routes of administration as a result of offered advantages such as better safety profiles, bioavailability and improved patient compliance has prompted the curiosity of researchers to search for new compounds or modify existing ones. The importance of selecting an appropriate method of synthesis and formulation of these compounds cannot be over-emphasized (Nadig, 2002; Li, *et al.*, 2005). The invention of a sample preparation method will influence the method's accuracy, repeatability and inter-laboratory reproducibility as well as its simplicity, adaptability, safety with time and cost-effectiveness (Nadig, 2002).

The method for the synthesizing polyamide 6,10 that can be modified to suit the intended use as a monolithic matrix system for rate-controlled drug delivery is based mainly on the knowledge of the chemical synthesis procedure which has an impact on the physicochemical and physicomechanical properties of polyamide 6,10. This experimental phase may pose some needless challenges if approached using the one-variable-at-a-time (OVAT) approach of scientific analysis. The OVAT approach is an un-systematic technique which involves separately changing the levels of each formulation or synthesis variable at a time and keeping all other variables constant in order to investigate the effects of specific variables on the selected response. Furthermore, this technique is not efficient and economical as it is time consuming and does not provide defined information about interactions between factors. It can at its best lead only to a local optimum of the system and in most cases, calls for unnecessarily numerous experimental runs that is not compatible with the rapidly rising costs of materials and often rely mainly on the experience of the researcher (Kincl, *et al*., 2005).

It is crucial that the development and optimization of the method of synthesis or preparation of polyamide 6,10 be accurately performed with as few experiments as possible. This can be achieved by using a statistically robust screening Plackett-Burman experimental design, the efficiency and reliability of which have been documented for the formulation of a wide range of pharmaceuticals (Singh, *et al.*, 1995; Karanchi and Khan, 1996; Wehrle, *et al*., 1996; Sastry, *et al*., 1996 and 1998; Bloomfield and Butler, 2000; Nazzal, *et al*. 2002; Nutan, *et al.*, 2005). The Plackett-Burman experimental design is usually described as a factorial design and it is often used to screen experiments by evaluating the main effects of the independent variables (factors) on the dependent variables (response). This design does effectively reduce the number of experiments required to identify and evaluate the main effects for further study. It is well adapted for this purpose because it enables the study of many factors with a few numbers of experimental runs (Sastry and Khan, 1998; Sibanda *et al*., 2004; Abdel-Fattah *et al.*, 2005; Li *et al.*, 2005; Goupy, 2005).

2.1.1. Objectives

In summary, the aim of this Chapter is to investigate and elucidate the effects (either antagonistic or synergistic) of altering the stoichiometry of the reactants (i.e. monomers) as well as the volume ratios of the immiscible solvents phases, employed for the dispersion of the reactants (partial modification), on the physicochemical and physicomechanical properties of the corresponding synthesized polyamide 6,10 variants. The Plackett-Burman experimental design was employed to synthesize polyamide 6,10 variants using the process of partially modified interfacial polymerization process. The usefulness of the statistical design (by applying the response surface methodology and one-way analysis of variance) in experimental elucidation and selection of significant factor variables to be incorporated into the higher performance Box-Behnken design template for optimization of the

physicochemical and physicomechanical properties of polyamide 6,10 to suit its intended application as a monolithic matrix system for rate controlled drug delivery was also be assessed. The physicomechanical parameters measured in terms of the matrix resilience (resistance to deformation), matrix hardness (measure of matrix rigidity) and deformation energy (work performed during matrix rupture) in which case matrix hardness and deformation energy will be concisely expressed as second-order polynomial hydrational rate constants will be employed as statistical response parameters. The effect of changes in pH of the hydration media on these parameters will also be explored as part of the screening process. Besides, the main effects and interaction plots will be used to mathematically visualize the influence of the factors (independent variables) on the responses (dependent variables) and compare the relative strength of the effects at the different factor levels and the mathematical interaction effects of the factors on the physicomechanical responses respectively. In addition, scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) studies will be used to correlate the effect of synthesis variables (i.e. stoichiometry and volume ratios) (partial modification) on the physicochemical and physicomechanical behavioural manifestations of polyamide 6,10 and to ensure the integrity of the chemical backbone configuration of the synthesized structures.

The overall outcome of this Chapter, which is based on the maximization of matrix resilience amongst the abovementioned physicomechanical parameters (matrix hardness and deformation energy), will be employed in the subsequent process interventions essential for fabricating the desired monolithic matrix system for rate-controlled drug delivery.

2.2. EXPERIMENTAL SECTION

2.2.1. Materials

Hexamethylenediamine (Mw 116.2), sebacoyl chloride (Mw 239.1), anhydrous n-hexane and anhydrous potassium bromide were purchased from Sigma Chemical Company (St. Louis, USA). All other reagents utilized were of analytical grade and used as received.

2.2.2. Synthesis of the Polyamide 6,10 variants in Accordance with the Plackett-Burman Experimental Design (Partial Modification)

Fourteen polyamide 6,10 variants were synthesized using various combinations of hexamethylenediamine, sebacoyl chloride, hexane and deionized water (independent variables) based on the statistically-generated Plackett-Burman design template. Tables 2.1 and 2.2 show the three levels of the independent variables used in the design and the experimental design template for the 4 factors and 14 experimental runs respectively. The lower and upper limits for the factors were set based on their ability to undergo optimal polymerization using minimal quantities of reactants.

Two solutions were prepared to synthesize each polyamide 6,10 variant. The first solution comprised specific quantities of hexamethylenediamine dissolved in deionized water i.e. the polar phase, while the second solution was composed of sebacoyl chloride evenly dispersed in hexane i.e. the non-polar phase. Table 2.2 provides the details of the exact quantities of monomers and solvents employed in the synthesis of each polyamide 6,10 variant. The two solutions were gradually added to form two immiscible phases (i.e. interfacial polymerization). A polymeric film (i.e. polyamide 6,10) formed at the liquid-liquid interface and was collected as a mass by rotating a glass rod at the interface of the immiscible liquids. The film was then thoroughly rinsed with deionized water (6×50mL), blotted on filter paper

(diameter 110mm and pore size 20µm) to remove any excess solvent and dried to constant weight at 40°C ± 0.5 for 96 hours in an oven (Memmert 854, Schwabach, Western Germany) . The chemical reaction equation specific for the synthesis of polyamide 6,10 by interfacial polymerization is presented in Figure 2.1 below.

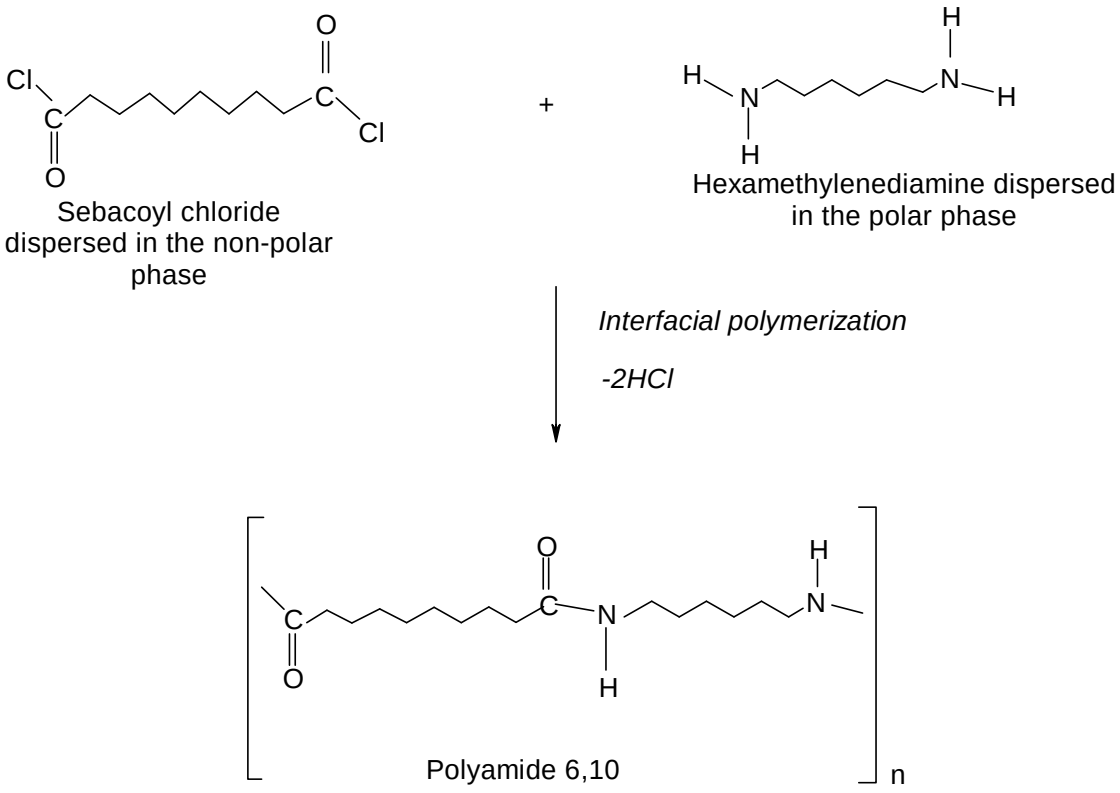


Figure 2.1: Synthesis of polyamide 6,10 by interfacial polymerization.

Table 2.1: Levels of the independent variables employed in the Plackett-Burman design

Independent Variables	Levels			Units
	Low	Middle	High	
HMD [a]	0.25	1.00	1.75	g
SC [b]	0.25	1.00	1.75	g
HEX [c]	10.00	25.00	40.00	mL
DW [d]	10.00	25.00	40.00	mL

[a] Hexamethylenediamine, [b] Sebacoyl chloride, [c] Hexane, [d] Deionized water

The percentage yield of each variant was calculated as a $\%^{w}/_{w}$ with respect to the stoichiometry of each chemical reaction. The mathematical relationship employed to calculate the percentage yield of each variant is stated below (Equation 2.1):

$$\text{Percentage Yield } (\%\,{}^{w}/_{w}) = \frac{\text{Actual Yield (g)}}{\text{Theoretical Yield (g)}} \times 100 \qquad \textit{(Equation 2.1)}$$

The theoretical yield was derived from the stoichiometry of the respective chemical reactions employed in the synthesis of each polyamide 6,10 variant while the actual yield was mass of the product (polyamide 6,10 variant) at the end of each synthesis.

2.2.3. Constructing the Experimental Design Template

A four-factor, three-level, Plackett-Burman design template was constructed for screening the monomer and solvent combinations (independent variables) to synthesize the polyamide 6,10 variants and to eventually select a suitable combination of factor levels generating the desired physicochemical and physicomechanical response characteristics. This design was selected because of its suitability for identifying key factors, with a minimum number of experimental runs, from the large number of factors for the desired response variables. These advantages make it extremely useful in investigational processes where the aim is to identify the reaction variables that have a major influence on the desired response. In addition, it can also be of use in preliminary studies where the aim is to identify formulation variables that can be fixed or eliminated for further investigations (Sastry and Khan, 1998; Abdel-Fattah, et al., 2005; Li, et al., 2005; Goupy, 2005).

The selected dependent variables (or responses) were the physicomechanical parameters namely: (i) the matrix resilience, (ii) matrix hardness and (iii) deformation energy hydrational rate constants. The quantitative physicomechanical performance of polyamide 6,10 was chosen as the response parameters for this experimental phase because of its substantial impact on drug release modulation, polymer matrix strength, degree of entangling and disentangling of the polymeric chain and its sensitivity to the polymerization chemical reaction (Pillay and Danckwerts, 2002; Cui, et al., 2004; Sibanda, et al., 2004). The factor levels for the independent variables and the design template are shown in Tables 2.1 and 2.2 respectively. The screening template was compiled using Minitab Statistical Software, Version 14 (Minitab Inc., USA), which required 14 experimental runs with two centre points (Table 2.2). The linear model established which encompassed 5 terms was as follows (Equation 2.2):

$$\text{Response} = b_0 + b_1[\text{HMD}] + b_2[\text{SC}] + b_3[\text{HEX}] + b_4[\text{DW}] \qquad \textit{(Equation 2.2)}$$

where the measured response (physicomechanical parameters) is associated with each factor level combination, b_0 to b_4 are the regression coefficients (b_0 is an intercept or a constant) and hexamethylenediamine [HMD], sebacoyl chloride [SC], hexane [HEX] and deionized water [DW] are the independent variables.

Table 2.2: Plackett-Burman template generated for 4 factors

Experimental Runs	Quantities of Reactants			
	HMD (g) [a]	SC (g) [b]	HEX (mL) [c]	DW (mL) [d]
1	1.75	1.75	10.00	40.00
2	1.75	0.25	10.00	10.00
3	0.25	1.75	10.00	10.00
4	1.00	1.00	25.00	25.00
5	0.25	1.75	40.00	40.00
6	1.75	1.75	10.00	40.00
7	0.25	0.25	40.00	40.00
8	0.25	1.75	40.00	10.00
9	1.75	0.25	40.00	10.00
10	0.25	0.25	10.00	40.00
11	1.75	0.25	40.00	40.00
12	1.00	1.00	25.00	25.00
13	1.75	1.75	40.00	10.00
14	0.25	0.25	10.00	10.00

[a] Hexamethylenediamine, [b] Sebacoyl chloride, [c] Hexane, [d] Deionized water

2.2.4. Determination of the Physicomechanical Parameters of Polyamide 6,10 Variants by Textural Profile Analysis

Textural profiling was employed to elucidate the physicomechanical characteristics of the polyamide 6,10 variants in terms of their matrix resilience as well as the hydrated and unhydrated matrix hardness and deformation energy. Analysis was conducted on both unhydrated and hydrated polyamide variant matrices to evaluate the influence of changing reaction stoichiometry and solvent volume ratios on textural transitions associated with the dynamics of differential matrix hydration.

A calibrated Texture Analyzer (TA.*XTplus*, Stable Micro Systems, England) fitted with a cylindrical steel probe (50mm diameter; for matrix resilience) and a flat-tipped steel probe (2mm diameter; for matrix hardness and deformation energy) was employed for these purposes. Data was captured at a rate of 200 points per second via Texture

Exponent Software (Version 3.2). The parameter settings employed for the analysis are outlined in Table 2.3.

Samples of each synthesized solid polyamide 6,10 variants (150mg) presented as compact of (15mm×15mm) dimension was immersed in 100mL deionized water and buffered solutions of pH 3 and 7.4. Samples were then removed after 2, 4, 6 and 8 hours of exposure to the hydration media and analyzed for variations in matrix hardness (N/mm) and deformation energy (Joules or Nm). Matrix resilience (%) was calculated only for the unhydrated samples.

Table 2.3: Textural settings employed for the determination of matrix hardness, deformation energy and matrix resilience

Parameters	Settings
Pre-test speed	1mm/sec
Test speed	0.5mm/sec
Post-test speed	1mm/sec
Compression force [a]	40N
Trigger type	Auto
Trigger force	0.5N
Load cell	50kg
Compression strain [b]	50% strain

[a] *Used for matrix hardness and deformation energy*
[b] *Used for matrix resilience*

Typical force-distance and force-time profiles generated for computation of the textural parameters are shown in Figure 2.2. Figure 2.2a depicts a typical force-distance profile for computing the matrix hardness (N/mm), which is provided by the gradient between the initial force (anchor 1) and the maximum force attained (anchor 2). Figure 2.2b depicts the area under the curve (AUC) of a force-distance profile used to calculate the matrix deformation energy (J). Figure 2.2c depicts a typical force-time profile used to calculate the matrix resilience which is represented by the percentage

of the ratio between the AUC of anchors 2 and 3 ($AUC_{2,3}$) and anchors 1 and 2 ($AUC_{1,2}$).

2.2.4.1. Determination of the Physicomechanical Hydrational Rate Constants

In order to evaluate and elucidate the effects of hydration time and pH of each media (deionized water and buffered solutions of pH 3 and 7.4) on the physicomechanical consistency of the polyamide matrices, changes in the matrix hardness and deformation energy with hydration time (2, 4, 6, 8 hours) were evaluated. The intrinsic values obtained at each time point from textural profiling were fitted to a second-order polynomial from which the physicomechanical hydrational rate constants were calculated. This approach provides a concise effect of the hydration process on the physicomechanical integrity of the polyamide 6,10 matrices which is relevant for drug delivery purposes. A correlation coefficient (R^2) value was obtained for all curve-fitting, and was found to range between 0.90 and 1 for all parameters. Table 2.4 lists the symbolic representations and units for the physicomechanical hydrational rate constants used throughout this experiment. The computed values for each polyamide 6,10 variant are shown in Figure 2.3.

Table 2.4: Symbolic representations of the physicomechanical hydrational constants

Physicomechanical Hydrational Rate Constants	Symbolic Representations	Units
Matrix hardness in deionized water	kH_w	N/mm.hr
Matrix hardness in pH 3	kH_3	N/mm.hr
Matrix hardness in pH 7.4	$kH_{7.4}$	N/mm.hr
Deformation energy in deionized water	kE_w	Joule/hr
Deformation energy in pH 3	kE_3	Joule/hr
Deformation energy in pH7.4	$kE_{7.4}$	Joule/hr

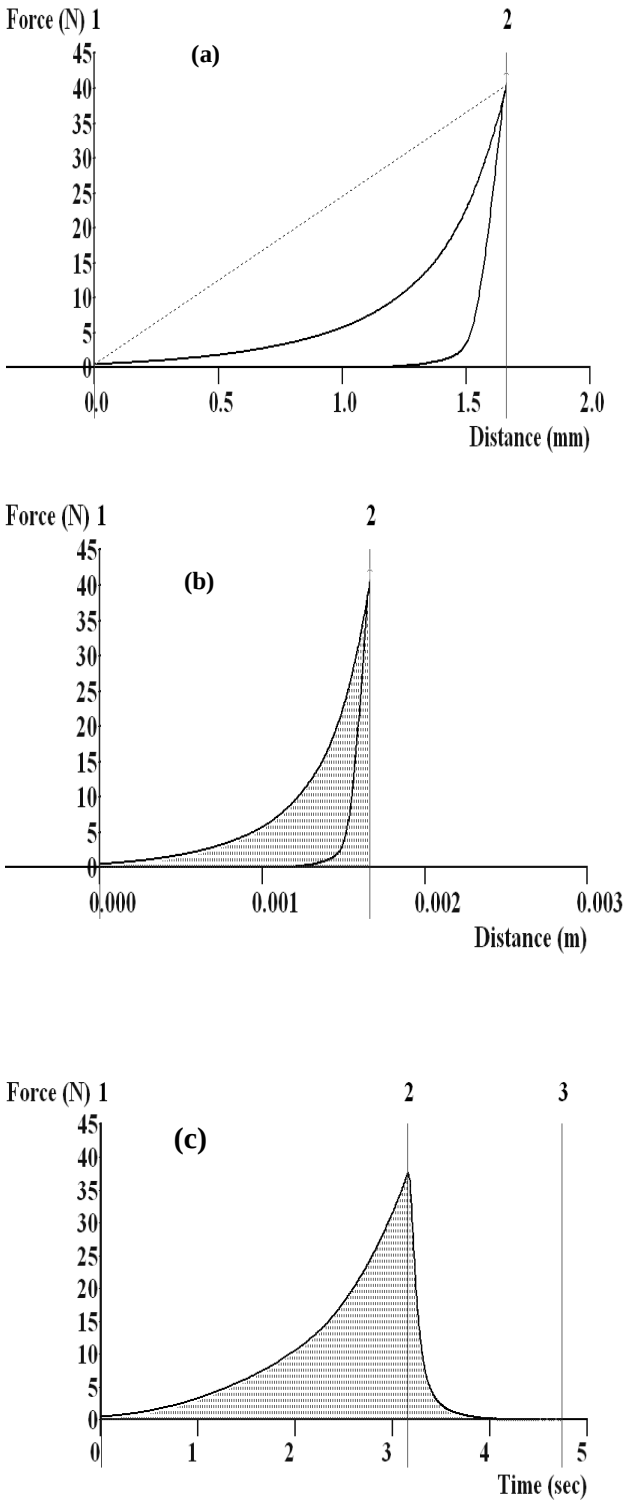


Figure 2.2: Typical force-distance and force-time profiles of polyamide 6,10 for determining both unhydrated and hydrated (a) matrix hardness, (b) matrix deformation energy and (c) matrix resilience (unhydrated only) (N=10 in all cases).

2.2.5. Determination of Functional Group Vibrational Frequencies by Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra were recorded on a Nicolet Impact 400D Fourier infrared spectrometer (Nicolet Instruments Corporation, Madison, USA) equipped with Omnic Version 3 FTIR software. Powdered samples of the respective polyamide 6,10 variants were used to prepare transparent potassium bromide discs on a Beckman hydraulic press (Beckman Instruments, Inc., Fullerton, USA). Background spectra were collected before running each sample. Samples were analyzed at wavenumbers ranging from 4000 - 400 cm^{-1}. All scans were performed in triplicate.

2.2.6. Morphological and Qualitative Characterization of the Polyamide 6,10 Variants

The surface morphology of the polyamide 6,10 variants resulting from stoichiometric changes of the chemical reactants and variations in solvent volume ratio was monitored using Scanning Electron Microscopy (SEM) to identify the potential effect of these changes on the surface morphology of each variant. Samples (15mm×15mm) were sputter-coated with gold-palladium (to minimize the hydrophilic nature of the polyamides) and viewed under a JSM-840 Scanning Electron Microscope (JEOL 840, Tokyo, Japan) at a voltage of 20 keV and a magnification of 1000×.

2.2.7. Statistical Analysis of Data

A one-way analysis of variance and response surface methodology (Minitab V14, Minitab, USA) were performed on the generated data to analyze the statistical effects of variations in the reaction conditions, to compute the precision of the chosen experimental design and to eventually select a combination of factor levels that will maximize the physicomechanical characteristics of the polyamide 6,10 variants for its most superior features to suit rate-controlled monolithic drug delivery. The factor levels

of the monomers and solvents represented the independent variables while the physicomechanical parameters (i.e. matrix resilience and hydrational rate constants) represented the dependent variables (i.e. the response parameters).

2.3. RESULTS AND DISCUSSION

2.3.1. Synthesis and Physical Appearance of the Polyamide 6,10 Variants

The synthesized polyamide 6,10 variants appeared white, crystalline and as compact solids. When blended, they produced free-flowing, compressible white powders with varying consistencies. The yield of each variant was calculated and this ranged from 40%$^{w}/_{w}$ to 90%$^{w}/_{w}$ (Table 2.5). These showed that besides the stoichiometry of the reaction which is dependent mainly on the molar ratios of the combination of the reactants (i.e. the monomers), partitioning efficiency explained as the capability of the solute particles to segregate into the solvents, the volume ratios and polarity of the solvent systems employed in the synthesis, had marked influence on this physicochemical quality exhibited by the variants.

Table 2.5: Percentage yields of the polyamide 6,10 variants

Experimental Runs	Yield (%$^{w}/_{w}$)
1	86.00
2	67.50
3	53.55
4	40.11
5	79.87
6	80.70
7	60.00
8	69.00
9	48.25
10	75.00
11	89.00
12	77.00
13	90.54
14	70.11

2.3.2. Elucidation of the Effects of the Varying Factor Levels on the Measured Physicomechanical Parameters of the Polyamide 6,10

Regarding the different combinations of factors and their levels, considerably different values of the measured response parameters were obtained for each polyamide 6,10 variant. The numerical values of the responses extended over a wide range, from positive to negative values with reference to the respective parameter considered. The hydrational rate constants calculated for the matrix hardness plus the deformation energy and the unhydrated matrix resilience of the 14 experimental runs are shown in Figure 2.3.

2.3.2.1. Matrix Resilience

This is a measure of the elastic cohesiveness of the matrices and is defined as the capability of a strained body (e.g. the polyamide 6,10 variant matrices) to recover its dimensions after deformation caused by an external compressive stress (Jones *et al*., 1996; Pillay and Fassihi, 1999b). Generally, a decrease in the concentration of sebacoyl chloride and a corresponding increase in hexamethylenediamine coupled with a volume ratio of solvents maintained at 1:1 resulted in an increase in matrix resilience (15.1%). In addition, it was observed that at extremely low levels of solvents (i.e. 10mL), still maintaining a volume ratio of 1:1, lower levels of hexamethylenediamine and sebacoyl chloride yielded a higher matrix resilience value (18.1%). Two exceptional cases were noted in which hexamethylenediamine and sebacoyl chloride maintained at lowest (0.25g) and highest (1.75g) levels respectively with a 4:1 volume ratio (hexane:deionized water) and vice versa produced relatively higher values of matrix resilience (14.9% and 16.1% respectively) when compared with the highest (20.4%) in which case sebacoyl chloride and hexamethylenediamine (0.25g) as well as the solvents (10mL) with volume ratios of 1:1 were at the lowest levels.

2.3.2.2. Physicomechanical Hydrational Rate Constants for the Matrix Hardness and Deformation Energy

Hardness is defined as the force required to attain a given deformation of a body (e.g. polyamide 6,10). Deformation energy is the work (or energy dissipated) performed in Joules to overcome the adhesive and cohesive forces within the material. These parameters, which are measures of matrix rigidity or stiffness, were employed to view the effects of hydration in media of different pH on the integrity of the synthesized polyamide 6,10 variants.

The physicomechanical hydrational rate constants obtained produced both negative and positive values. The negative values described a decrease in the magnitude of either parameter from the original intrinsic value while the converse applied to the positive values. Due to the hydrophilic nature of the polyamides, the synthesized matrices absorbed the aqueous hydration media which resulted in chain unfolding and subsequent free energy changes within the hydrated structure. Conversely, for few matrices (e.g. sample 7), diffusion of the hydration media resulted in an increase in the magnitude of the hardness and deformation energy indicating that the interaction with deionized water molecules influenced by pH led to further chain unfolding or entanglement.

With respect to matrix hardness, as pH increased, a decrease and increase in the hexamethylenediamine and sebacoyl levels respectively as well as the solvent volume ratio of 4:1 (hexane:deionized water) produced positive hydrational constant values (e.g. samples 7, 8). This indicated that these combinations hindered matrix disentanglement even on hydration and hence may be more resilient. For the negative values (e.g. samples 2, 13), the reverse chain transitions was observed with volume ratios of either 1:4 (hexane:deionized water) or 1:1 especially at higher levels. A

similar trend was also observed for matrix deformation energy except that lower levels of hexamethylenediamine favoured matrix rigidity. Furthermore, volume ratios of 1:1 (maintained at lowest levels) and 4:1 (hexane:deionized water) generated the highest chain entanglement (e.g. sample 14). The opposite trends were observed for the negative values showing a decrease in matrix strength (e.g. sample 12).

It can be deduced from the observed trends that apart from the monomers which play a major role in determining the physicochemical and physicomechanical integrity of the polyamides 6,10 matrices, the solvents also contribute to matrix strength with higher levels of hexane increasing polymeric folding (strength) while the converse was true for deionized water. This was attributed to the hydrophobicity of hexane. Besides, the difference in the ionic composition of each buffer solution affected the penetration rate of buffer media into the polymeric structures and subsequently influenced the hydrational response of each matrix to the various media.

The numerical values of the matrix hardness and deformation energy hydrational rate constants as well as the matrix resilience of the 14 polyamide 6,10 variants are illustrated in Figure 2.3.

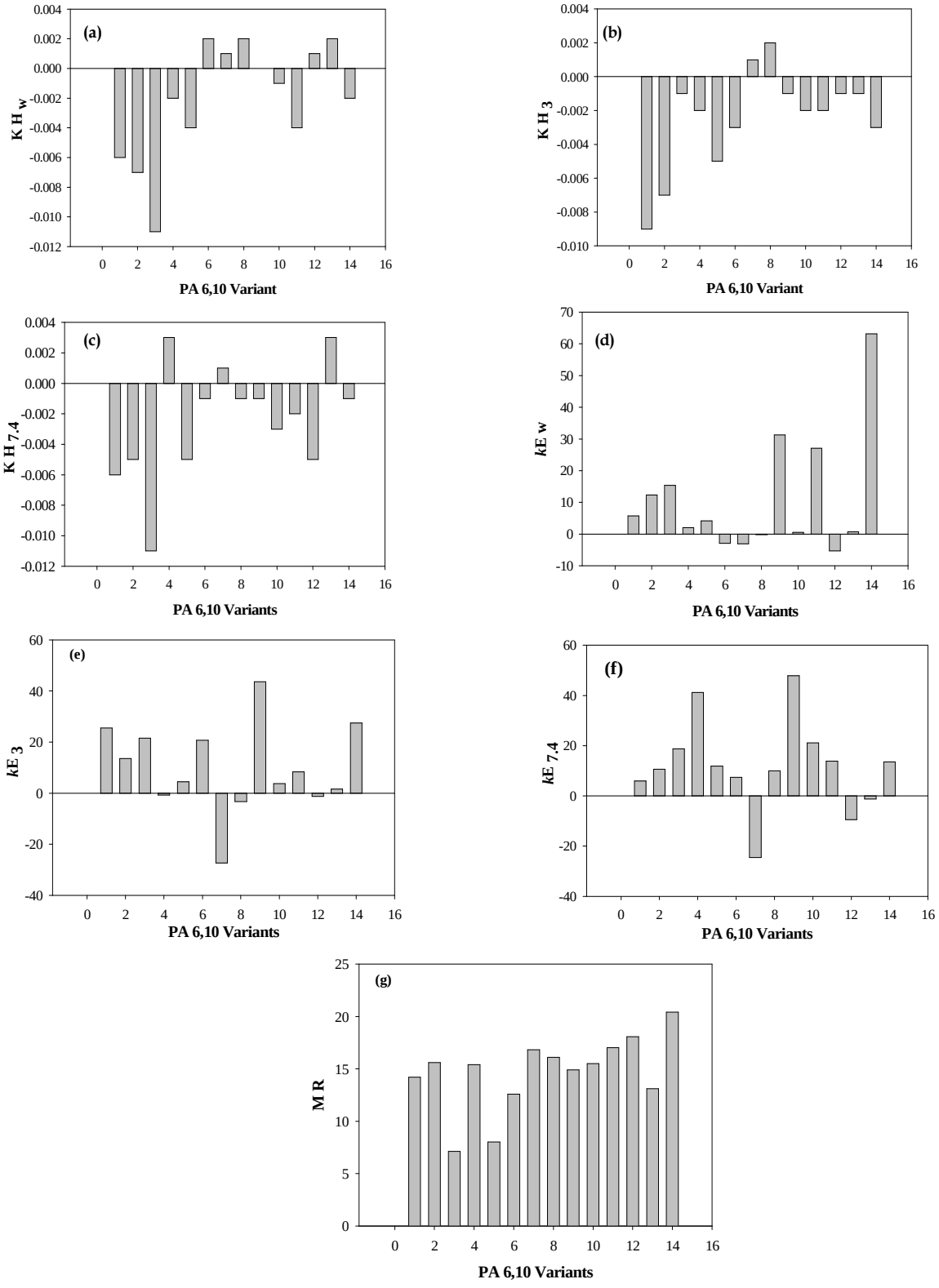


Figure 2.3: Physicomechanical hydrational rate constants and matrix resilience values of the different polyamide 6,10 variants (N= 10 and standard deviation less than 4.04 in all cases). ***Note****: PA 6,10 represent polyamide 6,10*.

2.3.2.3. Proposed Explanation of Observed Trends in Physicomechanical Parameters

The observed trends of the physicomechanical responses for each polyamide 6,10 variant are highly complex. Few explanations linked to the molecular kinetics and the solute-solvent interactions are outlined below:

(i) The differences in the stoichiometry of the chemical reaction which is determined by the concentrations of hexamethylenediamine and sebacoyl chloride (the solutes) involved in the synthesis of each polyamide 6,10 variant.

(ii) The diffusion velocity of the monomers (hexamethylenediamine and sebacoyl chloride) through the solvents (hexane and deionized water) to the reaction interface, which is affected by the volume, polarity, viscosity and the solute densities and solvents employed in synthesizing each polyamide 6,10 variant.

(iii) The solute-solute, solvent-solvent and solute-solvent (which vary for different molar combinations) surface characteristics that affect the stress-strain transitions and mobility patterns of the solutes (dynamic or static) towards the liquid-liquid interface.

(iv) The magnitude of the contact angle formed between the solute and solvent interface influenced by the level of solute wettability, molar concentration and solvent volume which may affect the orientation of the polar and non-polar ionic and covalent micellar molecular ends and forces of molecular interaction.

(v) Besides the established physicochemical characteristics of the solutes and solvents, the differences in their stoichiometry and volume ratios affects the entropy of the reaction system, that may also influences the partition coefficient and directly affect the rate and degree of partitioning of solutes into the organic phase where polymerization occurs.

2.3.3. Statistical Analysis of Data

2.3.3.1. The Analysis of Variance (ANOVA)

A one-way ANOVA was applied for estimating significance and reliability of the statistical model. The level of confidence accepted for this analysis was 95% where *p-values* less than 0.05 were considered significant. R^2 values of 0.90 and above were considered acceptable due to the complexity of the design. In addition, *p-values* for the lack-of-fit for all linear regression functions of each response parameter were greater than 0.05, suggesting that the model was accurate, stable and reliable. The Durbin-Watson statistic, d, an index that indicates the freedom of the models from serial correlation, ranged from 1.296-2.400 for all responses, which indicated that the linear regression function was accurate in predicting the responses. The statistical parameters utilized to assess the validity of the model for the respective responses are listed in Table 2.6.

All factors were statistically significant ($p<0.05$) showing that the independent variables (i.e. the different levels of the monomers and solvents) had a major influence on the explored physicomechanical parameters. In other words, this outcome suggested that the different factor levels (i.e. the stoichiometry of the reaction and volume ratios of the solvents) played a major role in determining the matrix integrity i.e. the degree of chain folding or unfolding during the process of hydration.

Table 2.6: Statistical descriptors for the different physicomechanical response

Response	R^2	Lack of fit (*p-values*)	Durbin- Watson (d)	Significance of terms (*p-values*)			
				HMD [a]	SC [d]	HEX [c]	DW [d]
kH_w	0.90	0.57	1.85	0.03	0.03	0.04	0.03
kH_3	0.92	0.85	1.90	0.02	0.02	0.04	0.03
$kH_{7.4}$	0.93	0.49	1.30	0.03	0.01	0.02	0.03
kE_w	0.99	0.08	2.35	0.01	0.04	0.01	0.02
kE_3	1.00	0.18	2.40	0.04	0.03	0.02	0.04
$kE_{7.4}$	1.00	0.77	1.32	0.04	0.04	0.04	0.04
M R	1.00	0.97	1.99	0.05	0.03	0.04	0.04

[a] *Hexamethylenediamine,* [b] *Sebacoyl chloride,* [c] *Hexane,* [d] *Deionized water*

2.3.3.2. Comparison of the Experimental and Fitted Response Values

The analytical procedure was employed to fit the values of the response parameters to evaluate the reliability of the model. A high degree of correlation between the fitted and experimental values based on the ANOVA for each response was evident that further revealed the accuracy of the statistical design. This is illustrated for all the responses in Figure 2.4.

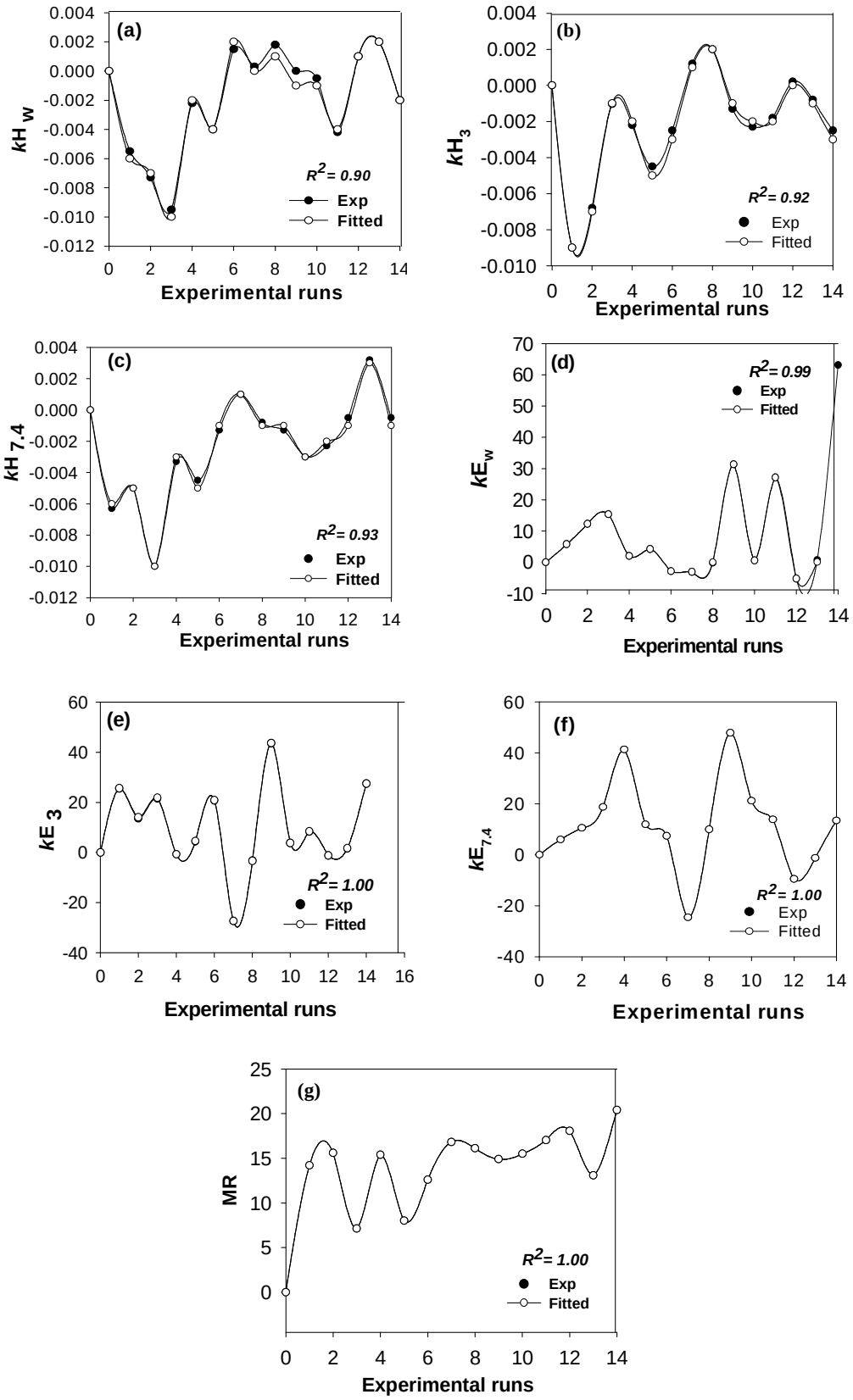


Figure 2.4: Comparison of experimental and fitted values for the responses (a) $k\mathrm{H}_w$, (b) $k\mathrm{H}_3$ (c) $k\mathrm{H}_{7.4}$, (d) $k\mathrm{E}_w$, (e) $k\mathrm{E}_3$, (f) $k\mathrm{E}_{7.4}$, and (g) MR. ***Note:*** $k\mathrm{H}_w$ – $k\mathrm{E}_{7.4}$ *are explained in Table 2.4 while MR represents the matrix resilience.*

2.3.3.3. The Main and Interaction Effects on the Responses

The main effects plots were employed to visually represent the influence of the independent variables on the responses and compare the relative strength of the effects at different factor levels (Figure 2.5a). It was observed that the mid-limit value for each factor (hexamethylenediamine 1g, sebacoyl chloride 1g, deionized water 25mL, hexane 25mL) produced a central point for changes (increase or a decrease) in the mean of all responses. Figure 2.5a for instance, demonstrates the synergistic effects of the independent variables (sebacoyl chloride, hexamethylenediamine, hexane and deionized water) on the response up to the mid-limit from where an increase in a factor level resulted in a decrease in the measured response with the reverse observed for hexane.

The interaction plots were used to visualize the mathematical interaction effects of the factors on the physicomechanical responses. Figure 2.5b illustrates the existence of interactions between the independent variables which could either lead to a decrease or increase in the magnitude of the measured responses. In other words, it can be stated that the effects of the different factor levels on the responses are not solely dependent on the individual monomer or solvent but also on their synergistic or antagonistic interactions on one another.

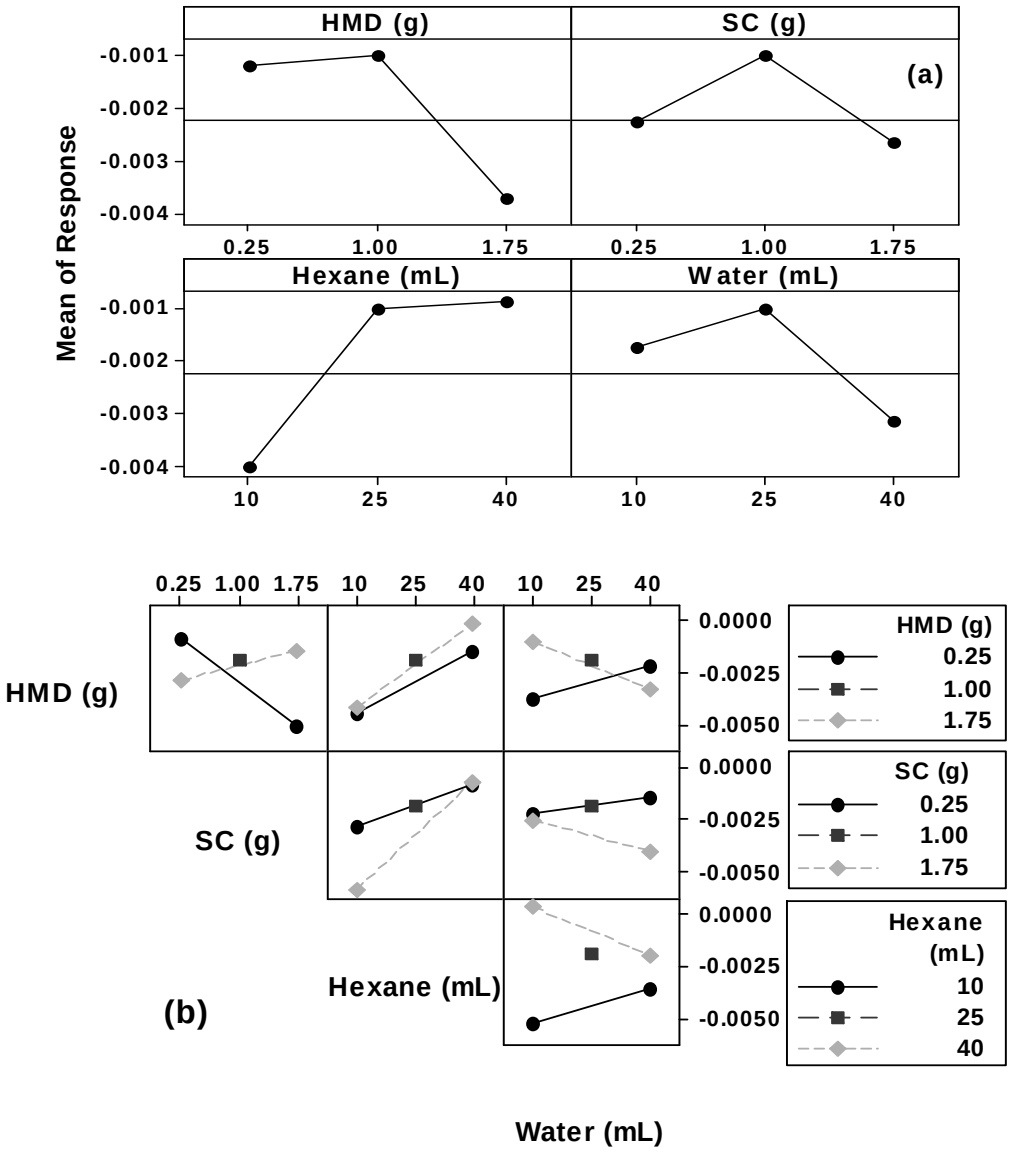


Figure 2.5: Typical (a) main effects and (b) interaction effects plots of the responses.

2.3.3.4. Three-Dimensional Surface Plots to Substantiate the Statistical Significance of the Effects of the Factor Levels on the Responses

Three-dimensional surface plots were utilized to further substantiate the significant effects of the factor levels (monomers and solvents) on the measured response parameters. Representative plots were selected for the respective response parameter and these are shown in Figure 2.6.

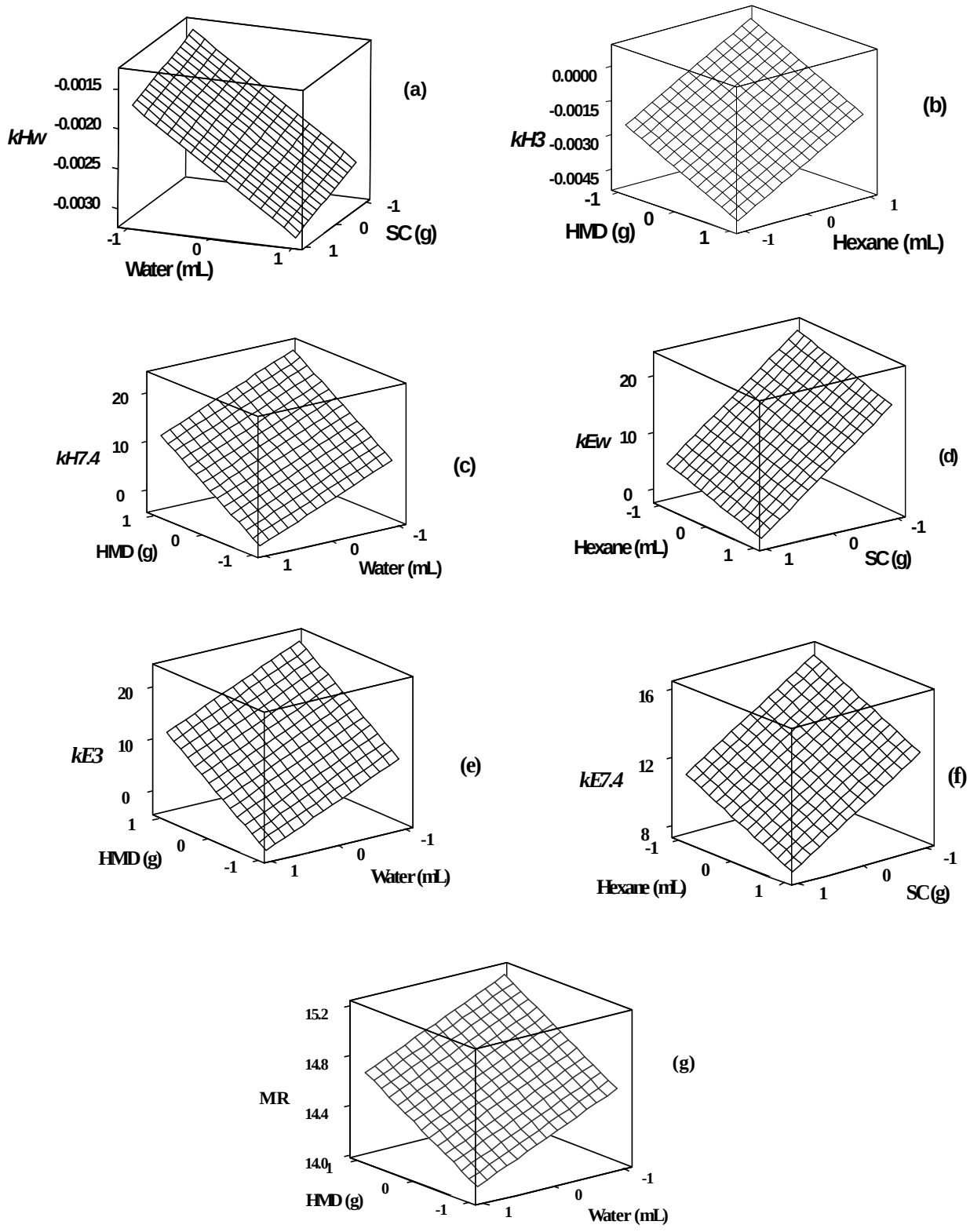


Figure 2.6: Three-dimensional surface plots for the response parameters: (a) $k\mathrm{H_w}$, (b) $k\mathrm{H_3}$ (c) $k\mathrm{H_{7.4}}$, (d) $k\mathrm{E_w}$, (e) $k\mathrm{E_3}$, (f) $k\mathrm{E_{7.4}}$, and (g) MR. ***Note**: $k\mathrm{H_w}$ – $k\mathrm{E_{7.4}}$ are explained in Table 4 while MR represent the matrix resilience.*

2.3.4. Maximization of the Matrix Resilience

In addition to the elucidation process as well as generating the linear regression equations relating the dependent to independent variables, polyamide 6,10 was optimized in terms of maximizing its matrix resilience using the regression equations (Equation 2.3).

Matrix Resilience = 14.653 + 0.282 [HMD] – 2.431 [SC] + 0.054 [HEX] – 0.267 [DW]

(Equation 2.3)

The matrix resilience was selected for maximization due to its large and direct impact on the overall polymeric matrix integrity and strength. Furthermore, the magnitudes of the matrix hardness and deformation energy, which are measures of the level of matrix rigidity, are also relatively dependent on the resilient nature of the polymeric matrix (Pillay and Fassihi, 1999b). Matrix resilience has been reported to have substantial impact on drug release characteristics and an increase in its magnitude improves matrix strength which can result in a reduction of the rate of drug release (Pillay and Danckwerts, 2002; Cui, et al., 2004; Sibanda, et al., 2004).

In this study the maximal experimental parameters were determined using the three-dimensional response surface plots. Constraints (independent variables) were based on the factor level limits set in Table 2.1 in an effort to obtain an optimized polyamide 6,10 variant with a matrix resilience (%) greater than or closest to the realistically attainable value of 20% (Figure 2.3; i.e. the highest of the matrix resilience generated by sample 14). The experimental phase of the maximization process was subjected to identical conditions of synthesis and measurement (for matrix resilience) stated in Sections 2.2.2.1 and 2.2.2.3. The levels of the factors (hexamethylenediamine, sebacoyl chloride, hexane, deionized water) that achieved the desired matrix

resilience are depicted in Table 2.7. The experimental (23.02%) and predicted (17.65%) values were relatively close to the desired value of 20%.

Table 2.7: Optimal factor levels maximizing matrix resilience obtained by constraints applied on the independent variables

Selected factor levels				Maximized Response %		
HMD (g) [a]	**SC (g)** [b]	**HEX (mL)** [c]	**DW (mL)** [d]	**Pred** [e]	**Des** [f]	**Exp** [g]
1.75	0.25	40	10	17.65	20.00	23.02

[a] *Hexamethylenediamine,* [b] *Sebacoyl chloride,* [c] *Hexane,* [d] *Deionized water,* [e] *Predicted value,* [f] *Desirable value,* [g] *Experimental response*

2.3.4.1. Response Surface Plots to Explain the Significant Effects of the Factors on the Matrix Resilience

Presenting the optimized experimental results in the form of three-dimensional surface plots, Figures 2.7a and 2.7b indicates that higher levels of hexane and hexamethylenediamine increased matrix resilience. On the other hand, Figure 2.7b depicts that higher values of matrix resilience were attained with decreasing concentrations of sebacoyl chloride and deionized water.

A proposed chemical explanation to this mathematical interpretation is that an increase in the level of hexamethylenediamine and hexane significantly increased the potential of the polymeric matrix to form a stronger and more compact network (crystalline lamellar structure) due to the hydrophobicity of hexane and sebacoyl chloride and the hydrophilic tendencies of hexamethylenediamine and furthermore enhanced by the hydrophobic nature of sebacoyl chloride. A high volume of hexane protects the ionic moiety (i.e. the chloride ion; Cl^-) in sebacoyl chloride from hydrolysis to sebacic and hydrochloric acid, which may reduce the rigidity of the polymeric backbone.

Maintaining sebacoyl chloride at the lowest level stabilizes its contact with the polar liquid. The complementary effects of hexamethylenediamine and sebacoyl chloride maintain the maximum level of polymeric hydration, enhancing molecular packing. As much as deionized water has the capacity to decrease matrix firmness, minimum levels are required in retaining a maximal level of matrix flexibility by maintaining the inter-chain hydrogen bond interactions, which suppresses the shear slip of the polymeric chains during deformation thus increasing the elasticity of the polyamide structures. These physicochemical transitions synergistically combine to improve matrix strength thereby maximizing resilience.

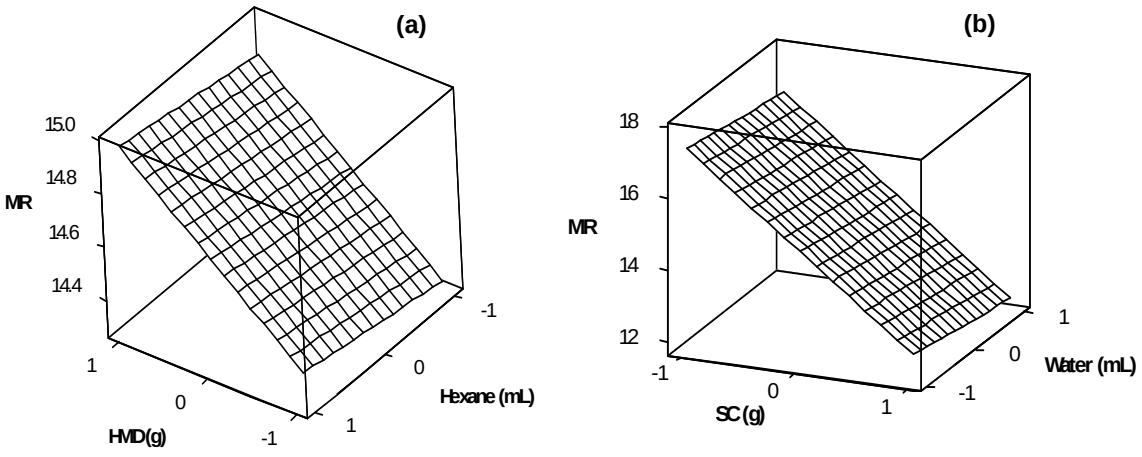


Figure 2.7: The three-dimensional surface plots showing the effects of the optimized factor levels on the matrix resilience: (a) effect of hexamethylenediamine (HMD) and hexane (b) effect of sebacoyl chloride (SC) and deionized water.

2.3.5. Fourier Transform Infrared Spectrophotometric Studies

FTIR studies were conducted on the polyamide 6,10 variants to assess the integrity of the structural backbone and identify salient functional groups. The major functional group absorption bands were consistent with the anticipated chemical composition (i.e. all showed characteristic methylene and amide absorption bands) (Table 2.8).

The successful integration of variations in physicochemical and physicomechanical properties of the polyamide 6,10 variant polymeric backbones were also substantiated by the subtle differences in vibrational frequency values of the salient functional groups attained by FTIR studies.

The subtle differences observed in the vibrational frequencies may be due to changes in the reaction stoichiometry and the solvent volume ratio interacting with the physicochemical and physicomechanical properties exhibited by the synthesized polyamide 6,10 variants. This may also be attributed to the varying effects of the aforementioned changes in the strength and length of the intramolecular hydrogen bond structures within the linear chains of the polyamides (Figure 1.1). This affects the electron cloud around the sigma (σ) single complex (saturated bonds) of methylene (—CH_2—) and amide (—NH—) groups along the chain, which subsequently affects the mobility of the pie (π) electrons (unsaturated bonds) of the carbonyl functional group (C=O). These structural alterations influence the vibrational frequencies, absorption bands and the peak intensities that may produce changes in the physicochemical and physicomechanical properties of the polyamide 6,10 variants (Table 2.8). A typical FTIR spectrum of a polyamide 6,10 variant is depicted in Figure 2.8.

Table 2.8: Vibrational frequencies of the polyamide 6,10 variants obtained from FTIR

Polyamide 6,10 Variants	C-H stretch	C-O	C=O	N-H	C-N	CH_2 wag	CH_2 rock
1	2933.66	1239.82	1707.72	3301.61	1189.82	1466.08	724.63
2	2927.24	1245.20	1708.81	3309.06	1331.46	1470.93	726.33
3	2919.03	1240.59	1607.80	3306.09	1301.88	1466.01	724.75
4	2932.58	1243.01	1701.31	3303.91	1302.21	1450.03	737.18
5	2933.64	1240.74	1702.27	3303.53	1301.90	1467.63	724.85
6	2932.92	1241.70	1697.36	3306.46	1302.04	1466.32	736.52
7	2962.78	1244.76	1720.01	3308.72	1308.58	1466.67	723.24
8	2931.93	1242.08	1702.25	3304.67	1302.27	1480.90	679.02
9	2937.60	1283.62	1701.88	3302.34	1319.97	1453.50	732.53
10	2930.89	1210.35	1705.78	3307.91	1323.63	1451.55	700.08
11	2928.01	1246.26	1736.21	3305.81	1321.13	1474.35	731.97
12	2928.09	1243.27	1698.39	3302.91	1343.05	1431.03	736.50
13	2927.50	1245.21	1687.31	3304.86	1331.85	1477.15	735.71
14	2928.62	1243.63	1695.77	3306.51	1326.29	1448.87	735.88
Select [a]	2970.81	1249.75	1705.11	3309.10	1289.77	1469.66	742.85

***Note**: Unit of measurements= cm^{-1}; [a] the selected polyamide 6,10 based upon the maximization of matrix resilience*

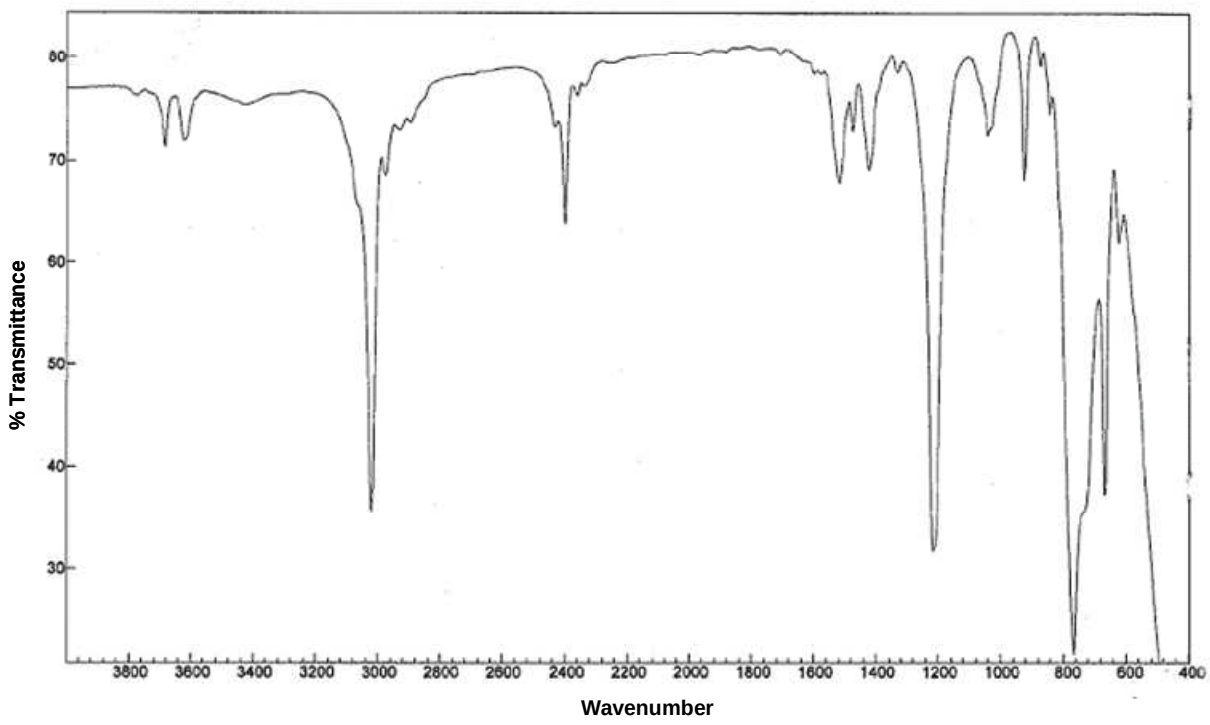


Figure 2.8: A typical FTIR spectrum of a polyamide 6,10 variant.

2.3.6. Surface Morphology of the Polyamide 6,10 Variants

This analysis showed that the differences in the surface morphology of polyamide 6,10 variants may play a critical role in altering their physicomechanical characteristics (Figure 2.9). A proposed explanation for this is the effect of the polymeric fiber surface morphology on the packing efficiency of the polyamide 6,10 variants monomer units producing a direct influence on the combined lamellar crystalline structure (a function of the chain folding and shear slip of the hydrogen bonded sheets) of the polyamide. The surfaces of the polyamide 6,10 variants were dissimilar in thickness, geometry, size and porosity. The exterior morphology of the different variants also varied from web-like (variant 9), wool-like (variant 1), ridge-like (variant 4 and 12), granule-like (variant 5), relatively continuous (variant 7), cluster-surfaced (variant 6) and scaly structures (variant 2 and 3). The morphological diversity in the surface of the polyamide 6,10 variants is illustrated with Figure 2.9. The conspicuous differences revealed in the micrographs showed the indicative effect of the changes in the stoichiometry of the chemical reaction as well as volume ratio on the structural configuration and consequently the physicomechanical behaviour of polyamide 6,10.

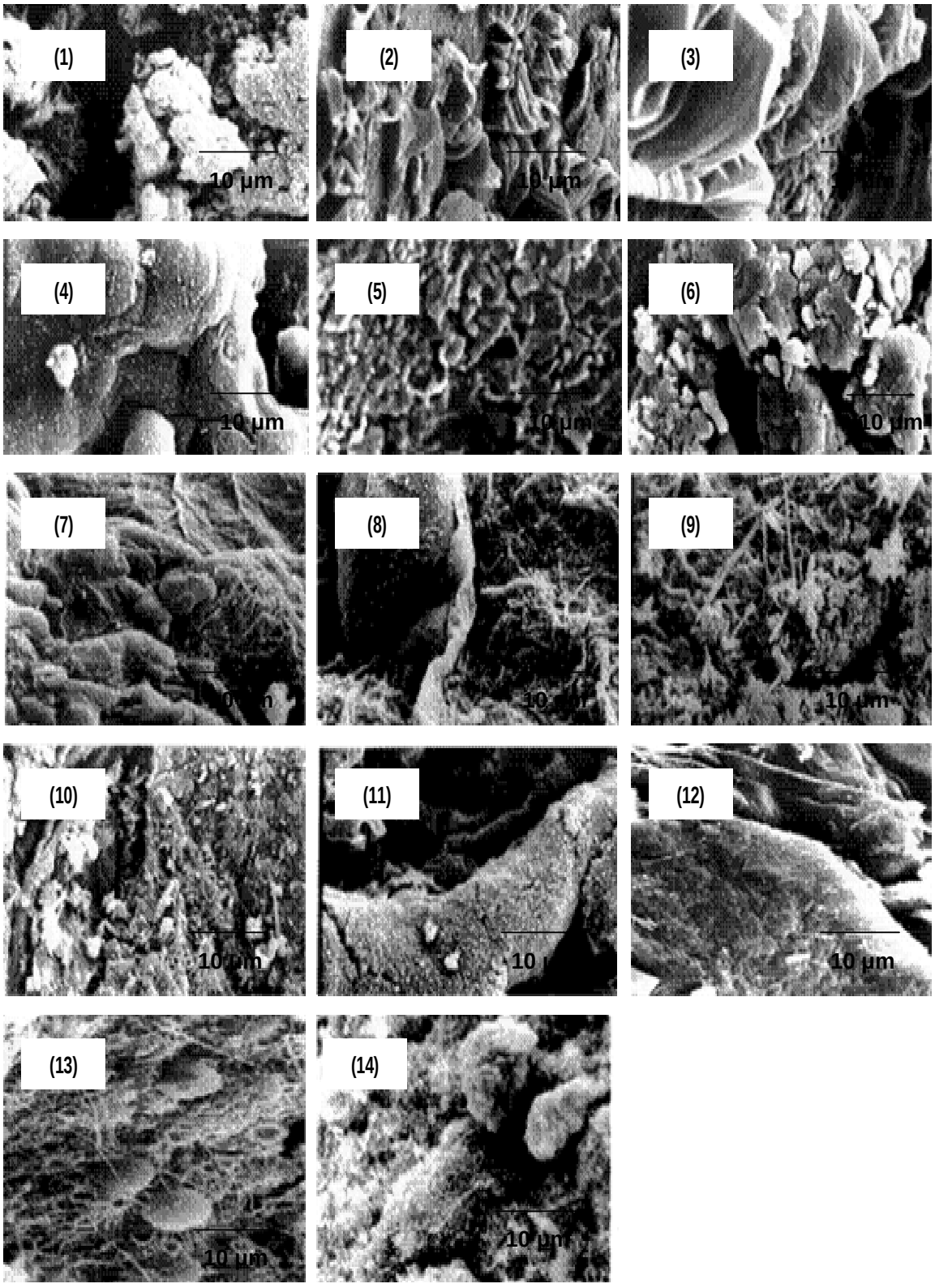


Figure 2.9: SEM micrographs of the fourteen variants showing the morphological diversity (Magnification x1000, voltage 20kV).

2.4. CONCLUDING STATEMENTS

This experimental phase has shown the reliability of the screening experimental design as a statistically and mathematically robust scientific tool. The design revealed a high level of variability that can be achieved in the physicochemical and physicomechanical properties of polyamide 6,10 as it relates to the influence of the different levels of the independent variables. ANOVA and three-dimensional surface plots indicated that the factor levels had significant effects ($p<0.05$) on the measured response parameters. As part of the screening process, a polyamide 6,10 matrix was selected based on the maximization of the matrix resilience. Matrix resilience was selected for maximization due to its significant impact on matrix integrity and drug release. In addition, the experimental and fitted values were closely correlated indicating the statistical design to be an accurate and reliable tool. Furthermore, the main effects and interaction plots were constructed to mathematically describe the influence of the independent variables on the responses and compare the relative strength of the effects at different factor levels on the response parameters. Fourier transform infrared spectroscopy (FTIR) identified the salient functional groups in the polyamide chain confirming the chain integrity in terms of the chemical structural backbone. Scanning electron microscopy (SEM) also revealed the diversity in the surface morphology of all the variants which may be responsible for the differences in their physicochemical and physicomechanical characteristics. On the whole, this phase forms a basis for further investigation on modifying polyamide 6,10 for possible applications as versatile rate-controlled drug delivery system. The efficiency of the partial modification strategy employed for this study was therefore established. In the next chapter, a full modification strategy involving changes in reaction stoichiometry, volume ratios and the solvent phase modifiers namely sodium hydroxide (NaOH) and cyclohexane will be carried out.