EFFECT OF SURFACTANTS ON THE MECHANICAL PROPERTIES OF ACETAMINOPHEN - WAX MATRIX TABLETS AND ITS IMPLICATION ON DISSOLUTION PROFILE.

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ABSTRACT:

The purpose of this study was to investigate the effect of non ionic surfactant on the mechanical properties of acetaminophen-wax matrix tablet and hence its implication on dissolution profile. Acetaminophen-wax matrix granules were prepared by melt granulation technique. This was formed by triturating acetaminophen powder (100g) with melted carnauba wax (20g), and with varying concentrations of polysorbate 80 or sorbitan monooleate (0-10%w/w) The molten mass was screened through sieves and air dried, hence drug to wax ratio was 5:1. The matrix tablets were formed by compressing the wax matrix granules at a constant load (30 arbitrary units on the load scale). The tablets were evaluated for tablet tensile strength, packing fraction, friability and *in vitro* dissolution profile. The dissolution data were analysed with different mathematical models namely zero order flux, first order, Higuchi, and Korsmeyer and Peppas equations in order to confirm the mechanism of drug release. All the tablets irrespective of concentration or type of surfactant used were compressible with tensile strength and packing fraction values between 1.47 to 1.63NMm^{-2} and 0.96 and 0.98 respectively. Their friability values were = 0.34%. The release rate increased with increase in concentrations of the non- ionic surfactants attributable to enhanced wetting of the solid dosage form by the presence of the surfactant. The analysed dissolution data revealed that the drug release fit first order flux and Higuchi square root of time model evident by their high correlation coefficient (r =0.93). The indication is that the drug release from these matrix tablets is by diffusion-controlled process. The mechanism of drug release was by anomalous (non-Fickian) diffusion indicated by their n values between 0.45 and 0.89. The study has shown that presence of non- ionic surfactants at an optimised concentration can be used to modulate the release of drug from wax matrix tablets.

Keywords: Wax Matrix Tablets, Non-ionic Surfactants, Tensile Strength, Dissolution Profile, First Order Flux and Higuchi Square Root of Time Model.

INTRODUCTION:

Hydrophobic waxy materials have been widely used in the formulations of different sustained release tablets, suspensions, beads, implants and microcapsules because of their chemical inertness, cost effectiveness, non- toxicity and more importantly their release retarding efficiency (Miyagawa et al, 1996). Some waxes that have been explored as carriers for sustained release applications include carnauba wax, bees wax, ceresine, microcrystalline wax, Precirol ATO5, Gelucire 64/02, goat fat and Compritol 888 ATO etc (Adeyeye and Price, 1991; 1994; Bodmeier et al, 1992; Uhumwangho and Okor 2006a; Inderbir et al, 2009).

Generally, carnauba wax is not used as binder in formulation of conventional tablets, though in its molten state it has been explored as binder to form sustained release tablets (Uhumwangho and Okor, 2006a). Its granules compact readily, forming hard compact even at low compression load (Uhumwangho and Okor, 2006b), this is attributable to the high plasticity of the wax. It also has great potential in ameliorating brittle fracture during tableting (Uhumwangho et al, 2009). Due to these attributes, carnauba wax was selected for this study. Surfactants are molecules that cause marked decrease in surface tension of solvents and are classified into cationic, anionic or non- ionic depending on the structure. They have wide applications in the pharmaceutical industries mainly as emulsifying, solubilising, wetting, foaming and antifoaming agents. Non- ionic surfactants such as polysorbate 80 or sorbitan monooleate are known to be non-toxic with good wetting ability. Thus, these were selected for this study.

Acetaminophen, an analgesic and antipyretic drug; indicated for the treatment of pains, headache and for the relief of fever was used as the test drug. The adult dose is 500 mg every 6 to 8h. It is a white crystalline powder, with a melting

point of 168° to 172°C. The chemical name is N-acetyl-*p*-aminophenol and its molecular weight is 151.16. Previously, Uhumwangho and Okor (2006a), evaluated the release of acetaminophen from carnauba wax matrix granules. However, the effect of surfactant on the release profile and mechanism of release was not investigated.

The aim of this study was to investigate the effect of different non- ionic surfactants on the mechanical properties of acetaminophen- wax-matrix tablets and its implication on dissolution profile. Another objective was to determine the drug release mechanism of this system. .

MATERIALS AND METHODS:

Materials:

Acetaminophen powder (Pharmaceutical grade) was selected as the test drug. Carnauba wax (Halewood Chemicals Ltd, England), a fine waxy solid with melting point of 82 - 88^{0}C and yellowish in colour was used as the matrix former for the granules. Non- ionic surfactants i.e polysorbate 80 (HBL 15) and sorbitan monooleate (HBL 4.3) were obtained from Sigma Aldrich Chemie Gmbh, Spain. These were used to modulate the drug release from the matrix tablets, while magnesium stearate (Qualikems Fine Chemical Pvt Ltd, India) was used as lubricant at a concentration of 0.5% w/w in the tablet formulations.

Methods

Melt granulation technique:

The wax material (20g) was melted in a stainless steel container in a water bath at a temperature higher than the melting point of the wax (i.e. 90^{0}C). Varying concentrations (0-10%w/w) of polysorbate 80 or sorbitan monooleate were added. A sample of the acetaminophen powder (100g) was then added to the melted wax with the different non- ionic surfactants and triturated with a Kenwood mixer. The mass was pressed through a sieve of 710m aperture size and dried in a vacuum oven (Model A2904, Gallenkamp, England) at 25^{0}C for 0.5h**.** The granules were stored in an airtight container before compression**.**

Tableting Technique:

The wax matrix granules were compressed using a single punch tableting machine (Manesty Type F3, Liver Poole, England) at constant load (30 arbitrary units on the load scale) to form flat faced tablets of diameter 12.5mm and weight 550±4.5mg with varying thickness. Immediately before compression of the granules, magnesium stearate (0.5%w/w) was incorporated. The tablets were allowed to equilibrate in a dessicator for 24h before their evaluation.

Determination of Tablet Tensile strength (T):

This is the stress that is needed to fracture a tablet by diametral compression. It is given by (Fell and Newton, 1970):

$$T = 2P/\ Dt \qquad (1)$$

where P is the fracture load that causes tensile failure of a tablet of diameter, D and thickness, t. The fracture loads (Kg) of ten tablets were determined individually with the Monsanto hardness tester, following Brook and Marshal (1968). The mean values of the fracture loads were used to calculate the T values for the various tablets.

Determination of Tablet Packing Fraction (P_f)

The tablet packing fraction (P_f) is a measure of the degree of consolidation or compactness of the tablet. It is given by the following expression (Itiola and Pipel, 1991):

$$P_f = w/\pi r^2 t\varrho \qquad (2)$$

where w is the weight of a tablet of radius, r, and thickness, t, and ϱ is the particle density. The tablet radius and thickness were determined using a digital micrometer. Ten tablets were used in each measurement. The apparent particle density of the was determined using a fluid (liquid paraffin) displacement method, details of which have been described elsewhere (Sugita et al, 1995). Essentially, the weight of a specific gravity (SG) bottle filled with liquid paraffin and the weight of the SG bottle containing a sample of the granule (1g accurately weighed) and then filled with liquid paraffin were determined. Liquid paraffin was used because it is a non-solvent for the test granules. The data were used to estimate the volume of liquid paraffin displaced, which was taken as the volume of drug sample. The determination was performed in triplicate, and mean results were used in the calculation of P_f.

Friability Test:

The friability test is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. Ten tablets were placed in the drum of an Erweka friabilator (Heusenstamm, Germany) rotating at 20 rev per min for 10 min. The percentage dust formed due to the impact was determined and taken as index of friability. The test was carried out in triplicate.

In vitro Dissolution Test:

The method described previously by Uhumwangho and Okor (2006a) was followed. In the procedure, one tablet was placed in a cylindrical basket (aperture size 425 m, diameter 20 mm; height 30 mm), which was immersed in 900ml of dissolution fluid (0.1 M hydrochloric acid maintained at 37 ± 2^{0}C). The fluid was stirred at 100 rpm with a single blade Gallenkamp stirrer (Model APP No. 4B 5784A). Samples of the dissolution fluid (5 ml) were withdrawn at selected time intervals with a syringe fitted with a cotton wool plug and replacing with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and were analyzed for content of acetaminophen spectrophotometrically at $_{max}$, 245nm (Model Spectronic 21D, Bausch and Lomvb, USA). The samples were filtered with Whatman No 3 filter paper before assay. The dissolution test was carried out in quadruplicate and the mean results reported. Individual results were reproducible to ± 10% of the mean.

Statistical Analysis:

All data obtained were subjected to student t- test ($p < 0.05$) to test for significance of difference between paired data.

Determination of Rate Order Kinetics:

The dissolution data were analyzed on the basis of zero order, (cumulative amount of drug released vs. time), first order rate (log cumulative amount of drug remaining vs. time), Higuchi model (cumulative amount of drug released vs. square root of time) and Korsmeyer and Peppas (log cumulative amount released vs time). These are the most frequently reported kinetics of drug release from drug particles and their solid dosage forms; see equations 3-6 (Higuchi, 1963; Korsmeyer et al, 1983; Peppa 1985; Harland et al 1985).

The kinetic models order equations are:

Zero order: $m = k_0 t$ (3)

First order: $\log m_1 = \log m_0 - 0.43\, k_1 t$ (4)

Higuchi: $m = k_H t^{1/2}$ (5)

Korsmeyer and Peppas dissolution model is of the form

$\text{Log } \%m = \log k_2 + n \log t$ (6)

where m is the percentage (%) amount of drug released in time t; m_1 is the residual amount (%) of drug in time t; m_0 is the initial amount of drug (100%) at the beginning of the first order release; k_0, k_1, k_2 and k_H are the release rate constants for the zero, first order, the Higuchi models and Korsmeyer and Peppas dissolution models respectively. The n is the diffusional release exponent that could be used to characterize the different release mechanism. For a tablet having cylindrical shape, n value below 0.45 indicates Fickian diffusion and n value between 0.45 and 0.89 indicates anomalous transport, often termed as first-order release. If the n value reaches 0.89 or above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the drug is released by zero-order mechanism. The correlation coefficient (r) for each rate order was also calculated.

RESULTS AND DISCUSSION:

Tablet Physical Parameters:

Tablet tensile strength values (T) were taken as measures of compressibility. All the formulated tablets were compressible with tensile strength, packing fraction and porosity values between 1.47 - 1.63NMm^{-2}, 0.87 0.91 and 0.09 - 0.13 respectively (See Table 1). However, there was no statistical significant differences between the T values ($p>0.05$) of the formulations irrespective of the concentrations or type of non- ionic surfactants used. This indicates that the presence of non- ionic surfactants in all the formulations did not affect the plastic deformation of the carnauba wax used as matrix former. The friability values of all the formulations were < 0.5% (Table 1) which indicates that they are within compendial specification of not more than 1% (US Pharmacopeia, 1995).

Table 1: Physicochemical Parameters of Tablets Prepared with Different Concentrations of Non Ionic Surfactant.

Concentration/type of surfactant (%w/w)	Tensile strength (NMm^{-2})	Friability index (%)	Packing fraction (P_f)	Porosity (1- P_f)
Polysorbate 80				
0	1.63	0.26 0.03	0.91	0.09
2.5	1.61	0.27 0.03	0.90	0.10
5.0	1.58	0.29 0.03	0.90	0.10
7.5	1.48	0.31 0.04	0.89	0.11
10	1.48	0.32 0.03	0.89	0.11
Sorbitan monooleate				
0	1.63	0.26 0.03	0.91	0.09
2.5	1.62	0.26 0.04	0.91	0.09
5.0	1.59	0.30 0.03	0.91	0.09
7.5	1.47	0.34 0.03	0.89	0.11
10	1.47	0.33 0.02	0.87	0.13

Table 2: Dissolution Parameters {m (%), t (h), m /t (%h^{-1})}of Tablets.

Concentration/type of surfactant (%w/w)	m (%)	t (h)	m /t (%h^{-1})
Polysorbate 80			
0	48	9	5.3
2.5	69	10	6.9
5.0	78	10	7.8
7.5	86	10	8.6
10	97	12	8.1
Sorbitan monooleate			
0	48	9	5.3
2.5	62	9	6.8
5.0	71	10	7.1
7.5	82	10	8.2
10	90	10	9.0

Table 3: Different Release Parameters of **Acetaminophen** (n=3) from Different Formulations when the Data were Analysed According to the Zero Order, First Order, Higuchi and Korsmeyer and Peppas Models.

Models	**Zero**		**First**		**Higuchi**		**Korsmeyer and Peppas**	
Concentration/type of surfactant (%w/w)	r	k_0	r	k_1	R	k_H	r	n
Polysorbate 80								
0	0.9539	5.3	0.9971	0.01	0.9907	17.1	0.9951	0.84
2.5	0.9298	6.7	0.9643	0.02	0.9969	22.4	0.9963	0.82
5.0	0.9479	6.9	0.9570	0.02	0.9923	23.6	0.9941	0.77
7.5	0.9686	8.3	0.9657	0.03	0.9894	28.5	0.9941	0.73
10	0.9859	8.0	0.9839	0.04	0.9264	30.7	0.9933	0.59
Sorbitan monooleate								
0	0.9539	5.3	0.9971	0.01	0.9907	17.1	0.9951	0.84
2.5	0.9051	6.4	0.9467	0.02	0.9891	20.1	0.9953	0.75
5.0	0.9260	6.8	0.9432	0.03	0.9896	21.7	0.9913	0.82
7.5	0.9555	7.9	0.9598	0.03	0.9942	26.7	0.9947	0.76
10	0.9714	8.7	0.9574	0.04	0.9872	29.7	0.9946	0.68

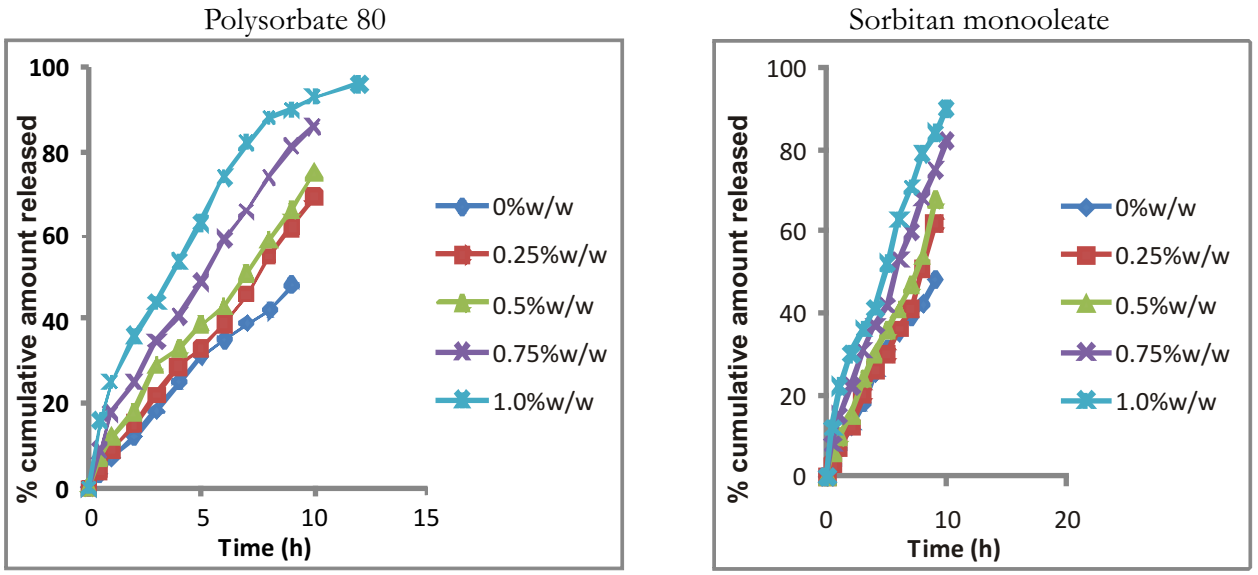

Fig 1: Influence of Different Concentration (0.0-10%w/w) and Types of Ionic Surfactants on the Dissolution Profiles of Acetaminophe Wax Matrix Tablets.

Release Profiles of Acetaminophen-wax Matrix Tablet.

The release profiles of acetaminophen -wax matrix tablets are presented in Fig 1. It was observed that the release profiles increased as the concentration of the two different non- ionic surfactants used in the formulation increased. This increase in release profile could be ascribed to the enhanced wetting of the drug due to the presence of the non- ionic surfactant during dissolution. This resulted in the formation of more channels for the dissolution fluid to leach out the drug from the matrix tablets since wetting is an important factor that controls matrix permeability. Furthermore, it may be attributable to the reduction in the interfacial tension between the drug and the dissolution fluid. It was observed that the increase in release profile was more with the polysorbate 80 compared with the sorbitan monooleate. However, the difference was not statistically significant ($p>0.05$). Tablet tensile strength can significantly affect the release rate of a drug (Capan, 1965), generally, an increase in tablet tensile strength is followed by a decrease in release rate, ascribed to a decrease in tablet porosity (Katikaneni et al 1995). However, the slight differences in release profiles from the different formulations could not be attributed to the tablet tensile strength or porosity since there was no statistically significant difference between these values ($p>0.05$). Perharps, it could relate to the differences in hydophilicity of the non- ionic surfactant used in the formulations, polysorbate 80 being more hydrophilic than sorbitan monooleate. The release parameters obtained from these curves are summarized in table 2. It can be observed that at 5.0%w/w of polysorbate 80 or sorbitan monooleate when incorporated into the matrix tablets, the maximum release (m_8), time to attain maximum release (t_8) and dissolution rate (m_8/t_8) were observed to be 78%, 71%, 10h, 10h and 7.8%h^{-1}, 7.1%h^{-1} respectively

Drug Release Mechanism

The dissolution data were further analysed to investigate whether they fit zero order flux, first order flux or Higuchi square root of time model. The analysed dissolution data revealed that the drug release fit first order flux and Higuchi square root of time model evident by their high correlation coefficient (r-values). The indication is that the drug release from these matrix tablets are by diffusion-controlled process. The correlation coefficients (r) and the release rate constants values are presented in table 3. The r values are 0.9051 to 0.9859 (zero order), 0.9432 to 0.9971 (first order), 0.9264 to 0.9969 (Higuchi). In order to understand the mechanism of drug release from this system, the power law was applied (Korsmeyer, 1983; Peppas, 1985). Their r and n values are presented in Table 3. Almost all the n values were between 0.45 and 0.89 which indicates anomalous transport, often termed as first-order release.

CONCLUSION:

The study has shown that presence of non- ionic

surfactants in an optimised concentration can be use to modulate the release of drugs from wax matrix tablets. The mechanism of drug release was by non-Fickian diffusion.

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