Nigerian Journal of Pharmaceutical Research
Vol. 8 No 1 pp. 255 - 269 (September 2010)

APPLICATION OF DIKA FAT IN THE FORMULATION OF HARD GELATIN CAPSULES WITH THE SOFT CENTRE

J. O. Onyechi
Department of Pharmaceutical Technology and Industrial Pharmacy, Faculty of Pharmaceutical Sciences,University of Nigeria, Nsukka.
Email: Jacob.Onyechi@unn.edu.ng

Abstract
The feasibility of using dika fat and some solid vegetable fats in the formulation of hard gelatin capsules with the soft centre was evaluated in this study. Phenylpropanolamine hydrochloride (PPA HCl) and chlorpheniramine maleate (CM) capsules containing dika fat (DF), stearic acid (STA), Lubritab (LB), Sterotex (STX) and Stearolac-S (STS) were prepared by the thermosoftening technique. Dissolution profiles of the formulations in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) showed that a measure of sustained release of the drugs was achieved over 8 hours and that drug release was by diffusion control. These fatty excipients may prove useful in this emerging technology for drug delivery.

Keywords: sustained release, hard gelatin capsules, dika fat, hydrogenated fatty acids.

INTRODUCTION

The restriction of hard gelatin capsules primarily to dry fills was a development only of the last century (Francois and Jones, 1979). The original patent on capsules describes them as applicable to both liquids and solids. The technology and formulation skills now exist to fill liquids or semi-solid dosage forms into hard gelatin capsules. Banding techniques used in sealing capsules and newer self-locking hard gelatin capsules (Hobs, 1894; FrP, 1963; FrP, 1966) and the development of high resting-state viscosity fills have made liquid/semi-solid filled hard gelatin capsules a feasible dosage form today (FrP, 1968).

Three conditions must be satisfied to successfully fill liquids and pastes into hard capsules. First, materials to be filled must not affect the empty shell and low moisture content materials are preferable. Second, encapsulating machines used to fill semi-solid materials must have the following features: a heated hopper to process thermosoftening mixtures and to reduce the working viscosity of thixotropic mixtures, a variable speed stirrer for the processing of thixotropic mixtures and to ensure the homogeneity of suspensions; an accurate liquid dosing pump with adjustable volume range, and a capsule handling system that removes filled capless capsules from other capsules.

*Corresponding author
ISSN 0189-8434

Some manufacturers with such machines include: Robert Bosch GmbH (Hofliger and Karg GKF/L range of machines); Harro Hofliger (KFM/L range of machines); Elanco (Rotop 8); Zanasi Nigris SpA (AZ 20/L machine range). Third, formulations to be filled into hard gelatin capsules should be pumpable to achieve reproducible dosage uniformity and should be solid in the capsule to avert product leakage on storage or handling. Three approaches are used to meet these formulation requirements, use of thixotropic, thermosoftening and a combination of thixotropic/ thermosoftening formulations.

Various excipients, used extensively in the formulation of other pharmaceutical products, have been suggested for the formulation of the hard capsule with the soft centre and include complex chemicals: vegetable oils, hydrogenated vegetable oils, vegetable fats and animal fats (Cuine *et al*., 1978); chemicals of known structure: hydrocarbons, fatty alcohols, fatty acids, esters, mixed esters, metallic stearates, silicones, silica derivatives and polyethylene glycols (Cuine *et al*., 1978).

Dika fat is a solid vegetable oil used for food and is generally regarded as safe. The purpose of this study was to evaluate the feasibility of the use of dika fat as well as other fatty materials, namely, stearic acid, Lubritab, Sterotex and Stearolac-S as excipients for the formulation of hard gelatin capsules with the soft centre containing. PPA HCl and CM were the drugs of choice.

MATERIALS AND METHODS

Materials

Dika fat was obtained from *Irvingia gabonesis var gabonesis* and *var excelsia* by soxhlet extraction as previously described (Udeala *et al*., 1980). The fat was further purified, bleached and deodorized (Onyechi, 1987). stearic acid (Baker Chemical Co, USA), Lubritab (Mendell, USA), Sterotex (Capitol city, USA) and Stearolac S (Paniplus, USA), PPA HCl (Merck, USA), CM (Hexagon, USA) and Aerosil 200 (Degussa, USA) were used as received from their manufacturers.

Methods

Differential Scanning Calorimetry, DSC

Thermal analyses were performed on dika fat, PPA HCl and 1:1 (w/w) physical mixture of dika fat and PPA HCl respectively. Thermal curves were obtained using a Perkin-Elmer DSC-4 Differential Scanning Calorimeter (Perkin-Elmer Corp., Norwalk, CT, USA) equipped with a Bascom Turner Recorder and Data Acqusition system (BASCOM Turner Instruments, MT, USA). After being firmly powdered, 2-8 mg samples of test substances were weighed out and encapsulated in an aluminium pan with crimp-on lids. Thermograms were obtained at a constant heating range setting of 20 mcal per minute, in an atmosphere of nitrogen and recorded at a constant chart speed of one inch per minute. PPA HCl and a 1:1 mixture of the drug and dika fat were heated over the temperature range 20 to 220^0C.

Preparation of PPA HCl and CM mixtures for capsule filling

*Corresponding author
ISSN 0189-8434

The composition of the formulations filled into the hard gelatin capsules is shown below:

PPA HCl	50 mg
Dika fat/Lb/STA/STX/STS	300 mg
Aerosil 200	50 mg
Beeswax	30 mg
CM	8 mg
DF/LB/STA/STX/STS	300 mg
Aerosil 200	50 mg
Beeswax	30 mg

PPAHCl and CM were the test drugs, Aerosol 200 was used to give structure to the mass, beeswax to solidify mixture, and Dika fat, LB, STA STX and STS the fatty matrix material.

The quantities of material for 50 capsules were prepared in any one batch. This number gave sufficient material for all the tests required. In the preparation of the formulations, the amount of dika fat required was weighed out as well as beeswax and heated with gentle heat till molten. The drug PPA HCL or CM was added with stirring. Aerosil 200, bolted through a No. 40 mesh, sieve was added to the mixture with stirring. The resulting mass was homogenised to a smooth paste and filled into the capsules still warm.

UV analysis for PPA HCl and CM

Analytical techniques employed for the quantitative determination for drugs in delivery systems play a significant role in the evaluation and interpretation of data in dissolution studies. It is essential to employ well-characterised and validated analytical methods to yield reliable results which can be satisfactorily interpreted. The appropriateness of a technique is influenced by the ultimate objective of the study. The size of sample involved in the dissolution studies and the need for specificity, speed and economy influenced the choice of UV analysis in the work.

Analysis of PPA HCl

PPA HCl exhibits pH dependent stability. The spectrum of PPA HCl in 0.1N sulphuric acid shows peaks at 251 nm, 257 nm and 263nm respectively. In both SGF and SIF PPA HCl shows a peak at 262 nm. The UV spectrum of PPA HCl shows a peak in both SGF and SIF at 256 nm. Analysis for PPA HCl was therefore performed at this wavelength.

A stock solution containing 6.05 mg/ml PPA HCl in SGF was prepared. Aliquots of this solution were diluted with SGF to yield solutions with concentrations that varied from 0.15 to 0.91 mg/ml of PPA HCl. The stock solution of the drug in SIF contained 6.04 mg/ml. The absorbance of 0.12 to 0.73 mg/ml dilutions of the drug were measured at 256 nm. The standard curves for the determination of PPA HCl in SIF without pepsin and SIF without pancreatin gave linear plots with correlation of 1.0 respectively.

Analysis of CM

The UV spectrum of CM in SGF and SIF both exhibit a peak at 262 nm and the quantitative estimation spectrophotometrically was performed at this wavelength. A stock solution containing 1.0 mg/ml of CM in distilled water was prepared. The stock solution was diluted to yield solutions with concentrations that varied from 0.05 to 0.25 mg/ml, 0.05 to 0.35 mg/ml and 0.004 to 0.024 mg/ml in 0.1 N HCl, SGF without pepsin and SIF without

*Corresponding author
ISSN 0189-8434

pancreatin respectively. The absorbances of the solutions were measured at 262 nm and gave linear plots with correlation of 1.0 respectively.

Determination of drug content of the formulations

The PPA HCl content of the formulations was determined by accurately weighing and transferring quantitatively, 100 mg sample of material into a 500 ml volumetric flask. 25 ml of 0.001 M NaOH was added and warmed to 80^0C for 2 min in an ultrasonic water bath. The solution was cooled and made up to volume with 0.001 M NaOH. The resultant solution was filtered and assayed for PPA HCl content. The determination was repeated five times. The experiment was repeated for CM and replicated five times. The results are presented in Table 1.

Filling of hard gelatin capsules

The capsules were manually filled into size 0 capsules. A total of 20 capsules from each batch were filled. Two slips of wood were fixed parallel to, and at a little distance from, one another. The upper one was pierced with holes and covered with a strip of paper, in which suitable star-shaped incisions were made. The empty capsules were passed through the incisions in the paper and the perforations of the upper slip of wood until they rested on the lower slip. They were found to be held sufficiently firmly to allow them be filled with a plastic syringe.

Evaluation of the melting behaviour of the formulations

The BP method (McAdie, 1967) for the determination of melting point of substances was adapted for this determination. Thin walled (0.15 mm thickness) glass tubes made of hard glass and closed at one end were used. The closed end of the glass tubes was drawn into a reservoir to hold molten formulation mass.

Drug formulations previously prepared and allowed to solidify were "grated" into small particles and packed into the melting point tubes through the open end. Packing was effected by tapping tube and contents on a hard surface so as to form columns about 1 cm in height. Prior to the introduction of packed melting point tubes, the water in the heating vessel was heated to 30^0C. The hot plate which served as source of heating was then regulated to give a heating rate rise of 1^0C/min. The temperature at which sintering occurred was noted and that at which solid mass completely covered with liquid material or floated was also noted. The useful melting ranges were taken as the temperature range between sintering and complete immersion in liquid material. In the formulation of the dosage forms complete melting of all components is not desirable. Heat is applied to assist manipulation of the formulation mass and assist with filling into hard gelatin capsules. This melting range of the fill materials was determined in triplicates and is presented in Table 2.

Dissolution studies on hard gelatin capsule shells with the soft centre

The dissolution profiles of the capsules were determined using an automated Van der Kamp 600 six-spindle dissolution tester (Model 25, Beckman

*Corresponding author
ISSN 0189-8434

Instrument, USA). The dissolution medium was 1000ml of simulated gastric juice USP without pepsin or simulated intestinal juice USP without pancreatin maintained at 50 rpm.
Analysis of the drug content of the dissolution medium was performed in a UV spectrophotometer (model 25, Beckman Instrument, USA). Percent drug dissolved was determined from the Beer's law plot previously constructed. Dissolution studies were performed in triplicate for each batch of capsules. The dissolution data was plotted as percent drug dissolved against time.

RESULTS AND DISCUSSION

DSC experiments were undertaken to ascertain the compatibility of PPAHCl and CM with dika fat. Fig. 1 shows the thermal curves for PPA HCl, dika fat and a mixture of the drug with dika fat. The transition temperature range for the melting endotherm of pure PPA HCl is from 188-198^{0}C. The average maximum peak of transition is at 195^{0}C. This transition peak corresponds to the melting of PPA HCl. The thermal curve for the mixture of dika fat and PPA HCl (Fig. 1 c) combined the features characteristic of the curves for the dika fat (Fig. 1a) and PPA HCl (Fig. 1b). It has been stated that incompatibility is highly improbable if the thermal curve of a mixture is a simple superposition of those of the components. Incompatibility between dika and PPA HCl is therefore highly improbable.

The thermal curves for the mixture of dika fat and chlorpheniramine maleate (Fig. 2c) combines the features characteristic of the thermal curves of dika fat (Fig. 2a) and chlorpheniramine maleate (Fig. b). Interaction between dika fat and chlorpheniramine maleate is not expected when both are contained in the same dosage form.

Drug content and uniformity of drug distribution in capsules

The uniformity of drug distribution in each formulation was verified by calculating the coefficient of variation, CV of the drug content in the mixtures. The assay results are shown in Tables 1 and analysis of the result shows that the mixing technique employed in the formulation of the capsule mixtures was adequate. The mixtures were homogenous with CV ranging between 0 and 2.30.

Melting behaviour of formulations

The melting behaviour of the formulations was investigated to enable prediction of their handling properties during encapsulation. It was observed that sintering temperature depended on the matrix material used. It is probable that the temperature range observed in this study (Table 2) is indicative of the optimal handling temperature of the formulation mixtures. At that temperature range reported it was easy to manipulate each formulation mass in the manual filling method used. It has been stated that the important physical properties of the formulated mass are its viscosity, surface tension and melting

Table 1: Assay for drug content (mg/capsule) of formulations filled into capsules. n=6

*Corresponding author
ISSN 0189-8434

	PPA HCl	CM
STA	**50.28 (1.65)***	**9.11 (0.04)***
LB	**50.14 (1.25)**	**8.85 (1.12)**
STX	**49.52 (1.55)**	**9.06 (0.04)**
DF	**49.81 (0.91)**	**8.93 (0.67)**
STS	**49.58 (2.30)**	**9.23 (0.004)**

Table 2: Melting characteristics of formulations filled into capsules. n=3

	PPAHCl		CM	
Fatty Component	Sintering Temp (^oC)	Immersion Temp (^oC)	Sintering Temp (^oC)	Immersion Temp (^oC)
STA	61	65	60.5	67
LB	60	65	58	64
STX	58	63	59	63
DF	41	45	37	45
STS	60	63	59	63

*Corresponding author
ISSN 0189-8434

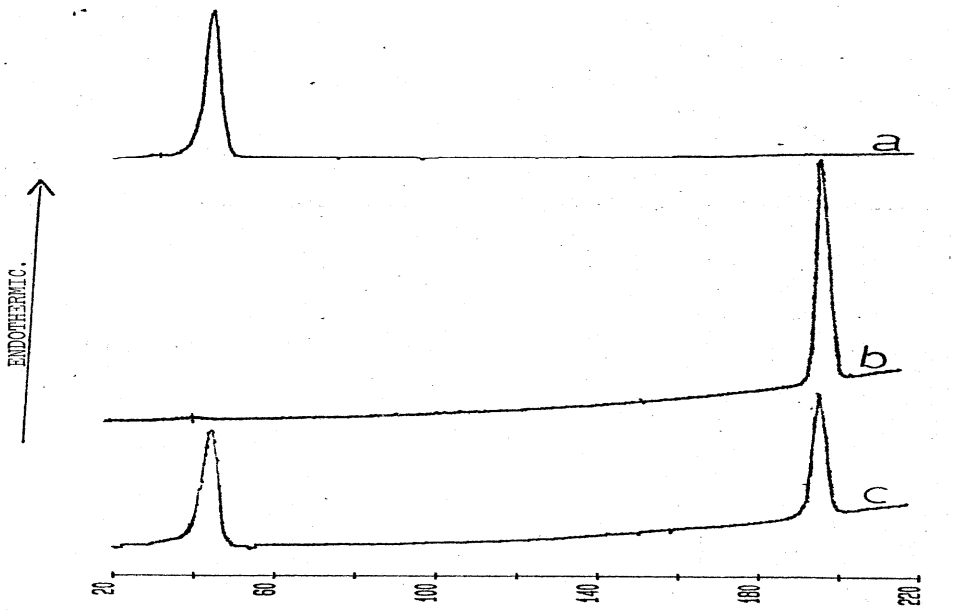

Fig. 1: DSC thermograms for dika fat and phenylpropanolamine hydrochloride.
a, dika fat; b, phenylpropanolamine hydrochloride and c, 1:1 mixture of dika fat and phenylpropanolamine hydrochloride.

*Corresponding author
ISSN 0189-8434

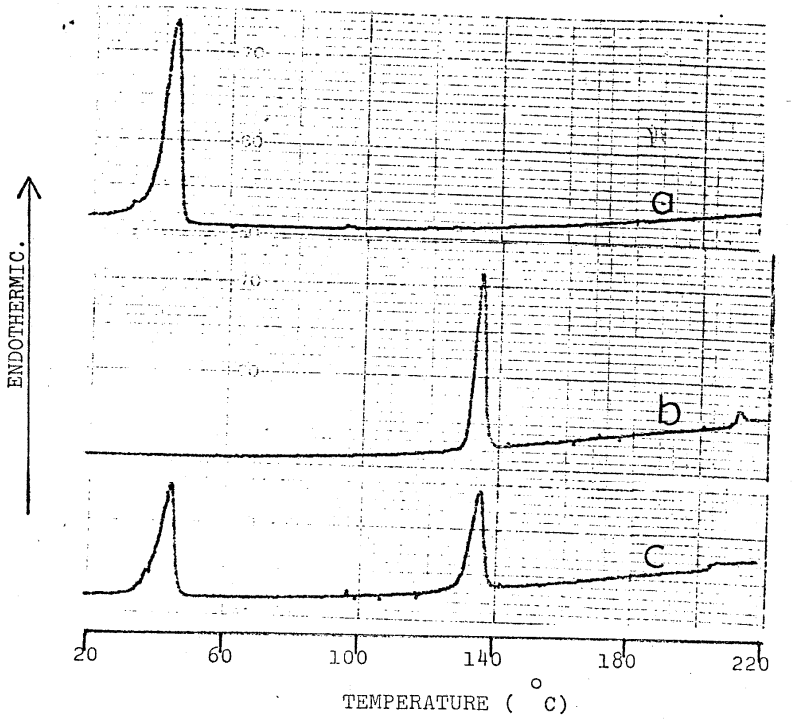

Fig. 2: DSC thermograms for dika fat and chlorpheniramine maleate. a, dika fat; b, chlorpheniramine maleate and c, 1:1 mixture of dika fat and chlorpheniramine maleate.

*Corresponding author
ISSN 0189-8434

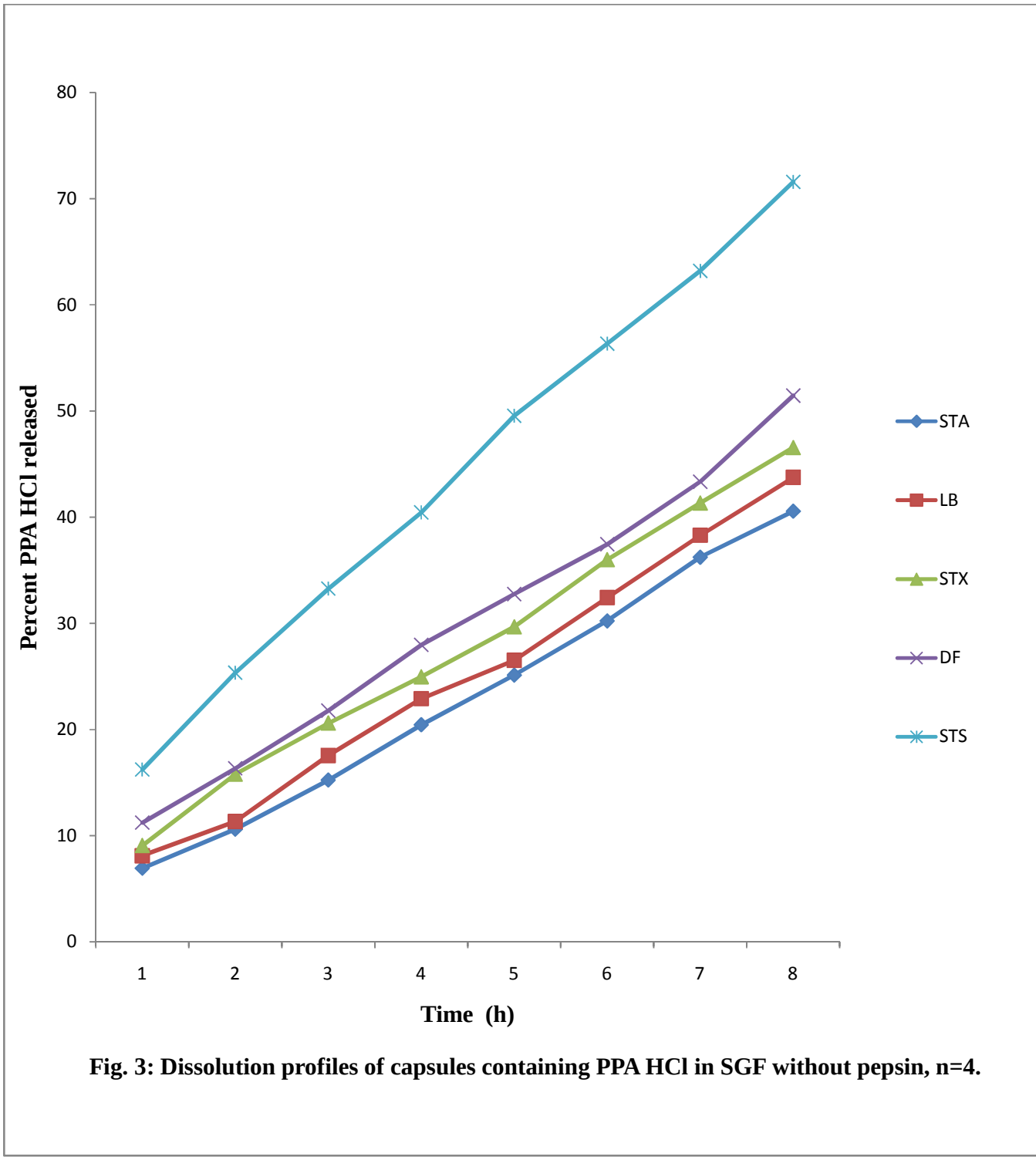

Fig. 3: Dissolution profiles of capsules containing PPA HCl in SGF without pepsin, n=4.

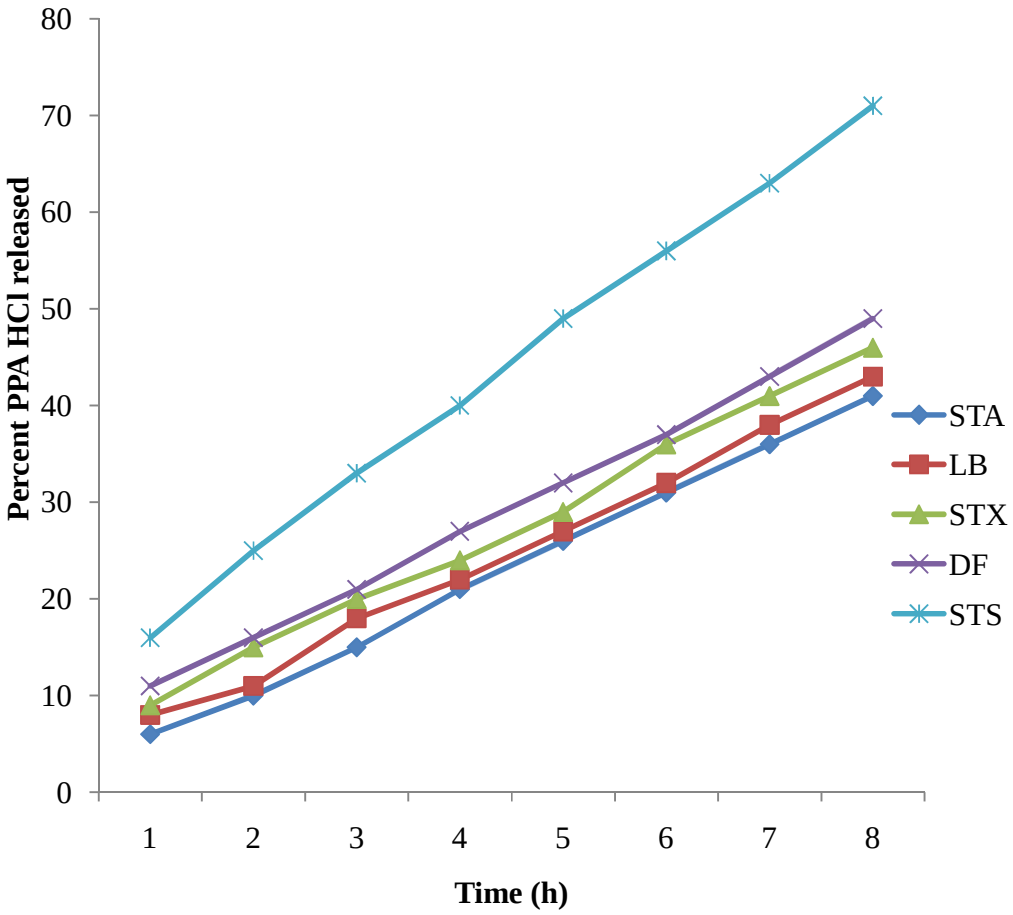

Fig. 4: Dissolution profiles of capsules containing PPA HCl in SIF without pancreatin, n=4

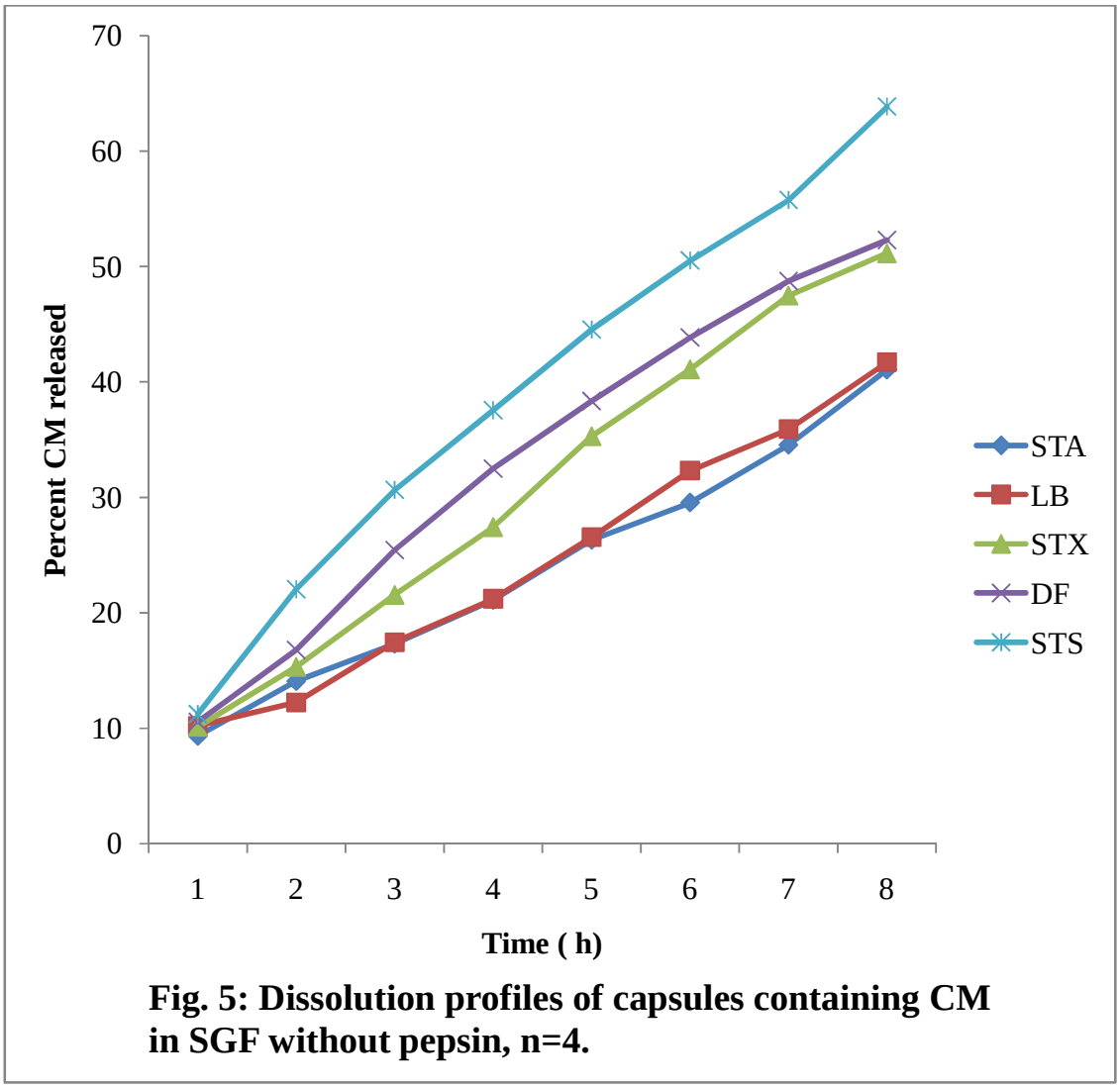

Fig. 5: Dissolution profiles of capsules containing CM in SGF without pepsin, n=4.

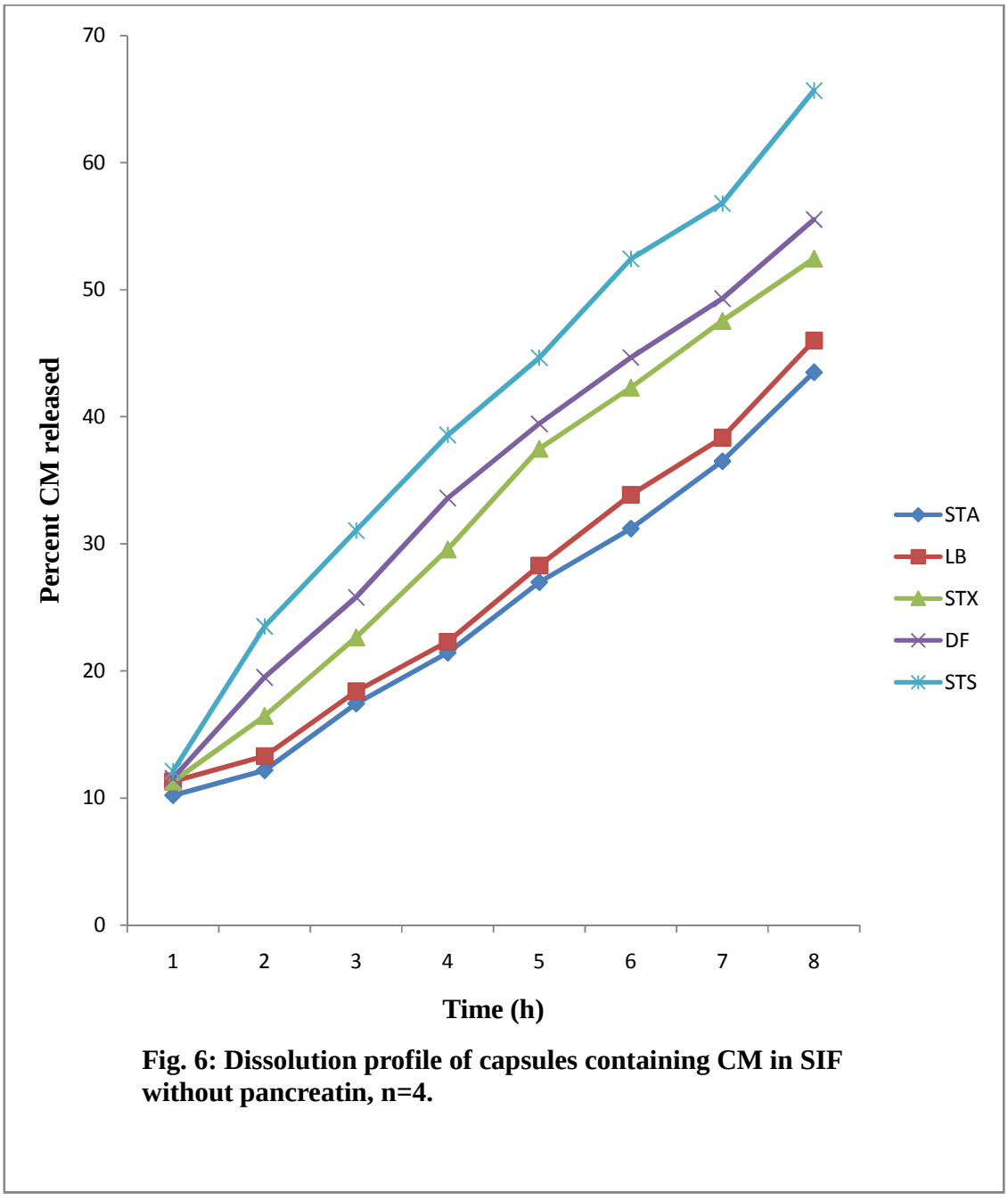

Fig. 6: Dissolution profile of capsules containing CM in SIF without pancreatin, n=4.

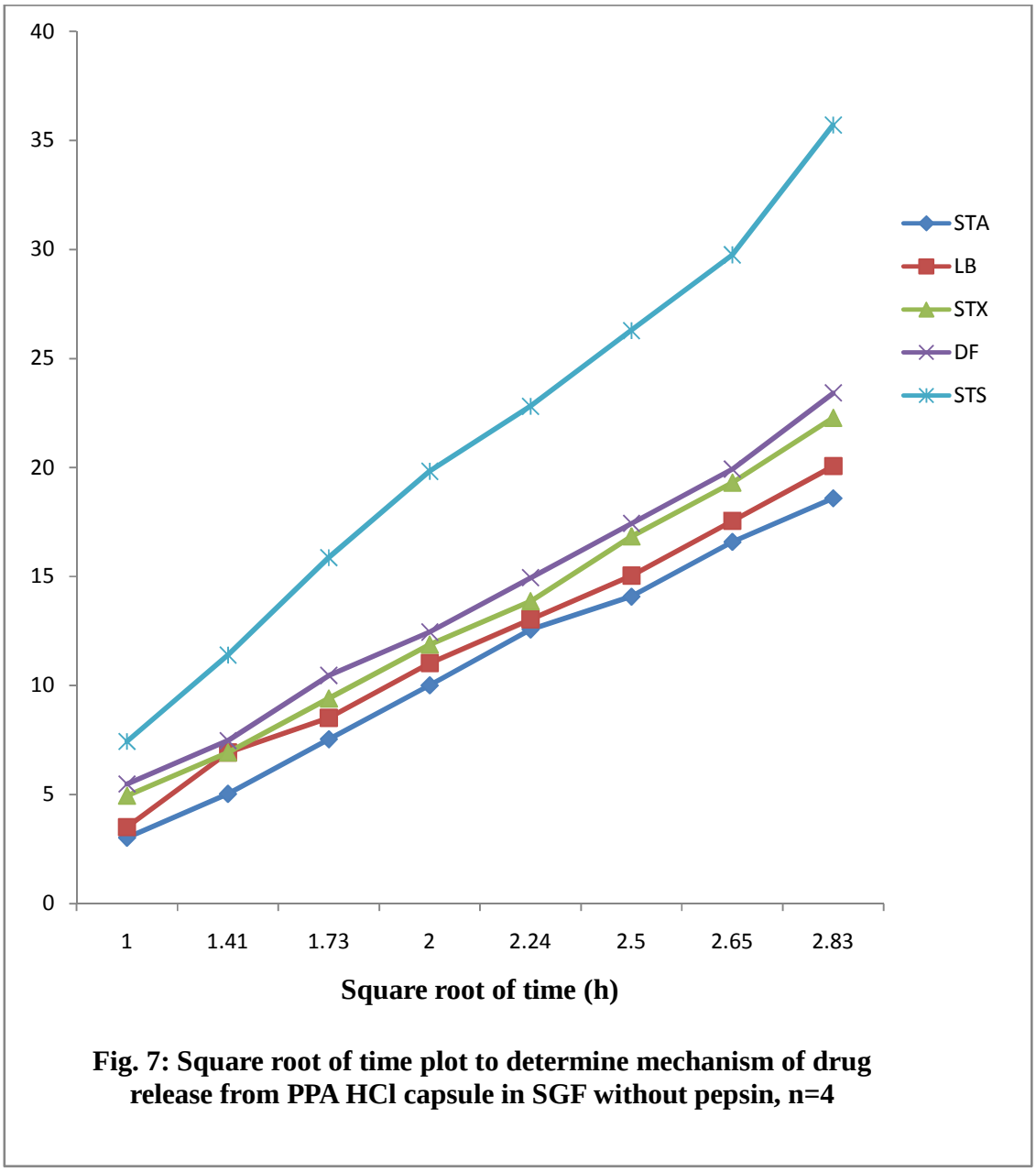

Fig. 7: Square root of time plot to determine mechanism of drug release from PPA HCl capsule in SGF without pepsin, n=4

point. The values of these will indicate how well the capsule product will withstand handling and storage.

Dissolution studies

The release of PPA HCl and CM from formulations is shown in Figs 3-6. Figures 3 and 4 represent PPA HCl release in SGF and SIF respectively While Figs 5 and 6 represent CM release in SGF and SIF respectively. In all the formulations sustained release of drugs were obtained. The factors which influence drug release from semi-solid formulations filled into hard gelatin capsules have been studied. Although published literature is limited because it is a new dosage form, factors which have been shown to significantly affect drug release include the established include the degree of hydrophobicity/lipophilicity of the formulation and the nature of the contents.

The primary aim of this study was a feasibility of the method using the fatty bases available to us. It was therefore necessary to suggest the main mechanism of drug release from the formulations. In this system, a solid drug was dispersed in insoluble matrix. The rate of drug release was dependent on the rate of drug diffusion but not on the rate of solid dissolution. Higuchi has described the appropriate equation describing drug release from this system as $Q = [De /T (2A – e C_s) C_s t]^{1/2}$ where Q= wt in grams of drug released per unit surface area; D = diffusion coefficient of drug in the release medium; e = porosity of the matrix; T = Tortuosity of the matrix; C_s = solubility of the drug in the release medium; and A = conc of drug in the tablet expressed as g/ml.

For purposes of data treatment the Higuchi equation reduces to $Q = k t^{1/2}$ and a plot of amount of drug released from the matrix versus the square root of time should be linear if drug release from the matrix is diffusion controlled. Drug release from all the formulations investigated in this study assumed similar shape and pattern and a typical plot of PPA HCl release from the matrix in SGF is shown in Fig. 7. The plot is linear and suggests that in all the dosage forms prepared and evaluated diffusion control is the predominant mechanism of drug release.

CONCLUSION

It is possible to use dika fat in the formulation of hard gelatin capsules with the soft centre. The ability to fill pastes and oils into hard gelatin capsules is now feasible and formulation techniques have been developed enabling conversion of drugs into masses with suitable physical properties. These masses can then be filled with automatic encapsulating machines hitherto used for filling powdered dosage forms, but now modified by being equipped with a fluid pump. Much of the oil/paste technology is subject of patents and patent applications. However, the development of this new dosage form offers formulation scientists potential in the safe handling of toxic materials, improved uniformity for potent drugs, improved stability for labile compounds and an easy way to design and produce controlled release products.

REFERENCES

Cuine, A. Mathis, C., Stamm, A. and Francois, D. (1978) Labo Pharma, Problems et techniques No 274: 222-7, Mise en gelues de solutions visqueuses des

principles actifs. 1: Etudes preilminaires – excipients
Fr P (1966) 1,461,033; BP (1968)1,133,715
Fr P (1963) 1,343,698; BP (1964) 970,761; USP (1965) 3,173,480
Fr P (1968) 1,103,629; Belg P 1971 (769,729)
Francois, D. Jones, B.E. (1979) Making the hard capsule with the soft centre. *Manufacturing Chemist and aerosol news*, 37 (3): 37-39
Hobbs, R.P. (1894) USP 525,844 and 525,845
McAdie, HG (1967) Anal. Chem., 39: 543
Onyechi, J.O. (1987) PhD Thesis UNN
Udeala, O.K., Onyechi, J.O. and Agu, S.I. (1980) J. Pharm. Pharmacol. 32: 6-9