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PREPARATION AND EVALUATION OF SUSTAINED-RELEASE MICROCAPSULES OF FLUOXETINE HYDROCHLORIDE

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ABSTRACT:

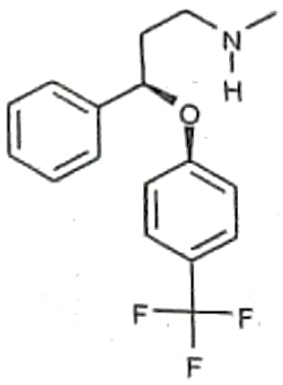
The aim of present work was to prepare and evaluate enteric coated microcapsules of Fluoxetine hydrochloride using cellulose acetate butyrate polymer (CAB) by the modified emulsion solvent evaporation technique. The effect of sustained release of CAB microcapsules was evaluated by an invitro dissolution test, and the results were compared to a commercial product (Prozac® capsules). The results showed that CAB microcapsules loaded with Fluoxetine hydrochloride can be easily prepared and encapsulation efficiency and loading capacity were about from 77- 98 and 11%. The retardation of the release rate was dependant on the coat /core ratio, as well as pH of the dissolution media.

INTRODUCTION

For the treatment of different diseases, it is possible to maintain constant blood and tissue levels over therapeutic range for an extended period of time. The design of any controlled–drug delivery system should satisfy these objectives. Controlled release may be defined as the process by which one or more active agents or ingredients are made available at a desired site in a suitable time and at a specific rate[1].

Microencapsulation is a well- known method that is used to modify and retard drug release from pharmaceutical dosage forms. Various microencapsulation techniques and coating materials may be employed to prepare the formed units[2,3]. According to microencapsulation procedure employed, coatings for microcapsules may contain several different additives such as film formers, plasticizers, and fillers. The most important material of coating is film former, which are high molecular weight polymers. These polymers may be sustained only like acrylic polymers and copolymers like Eudragit polymers, or enteric like shellac, cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP)[4,5,6]. Microencapsulation has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal irritation[7]. Microencapsulation provides a method of preparing drug delivery system to improve bioavailability, or stability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. Acetazolamide was microencapsulated using eudragit polymer to reduce side effects when compared with conventional dosage forms[8].

Fluoxetine hydrochloride, (±)-N-Methyl-3-phenyl-3-(α, α, α-trifluoro-p-tolyloxy) propylamine hydrochloride, is used as antidepressant of group selective serotonin reuptake inhibitors (SSRIs)[9]. Fluoxetine hydrochloride is most widely marketed as Prozac® (Eli Lilly) and it is commercially available in several countries as capsules, tablets or solution. In fact generic and galenic formulations of Fluoxetine hydrochloride have been marketed in 30 countries by at least 48 manufacturers and countless pharmacies[10,11]. Inhibitors of serotonin reuptake and result in both increased serotonin concentration at the synaptic cleft and autoreceptor stimulation[12,13]. Fluoxetine is a serotonin (5-hydroxytryptamine; 5-HT) re-uptake inhibitor widely used in the pharmacotherapy of endogenous depression. It targets membrane transporters in the central nervous system (CNS) thereby increasing synaptic concentrations of 5-HT molecules. Fluoxetine is characterized by a high affinity for brain serotonin transporter and by very low affinities for adrenergic, histaminergic, opiate, GABA and benzodiazepine receptors[14].



Many microencapsulation techniques have been developed for the coating of pharmaceuticals. Microencapsulation processes were classified as physical processes, chemical processes or mechanical processes[15]. The solvent evaporation method involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and, dissolved /dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size [16]. The principal controlling parameters of particle size of microspheres produced by the solvent evaporation technique are the speed of mixing, equipment, technique used for mixing the two phases, and the concentration of polymer in the dispersed phase[8,17]. In this study, cellulose acetate butyrate was used as retardants to prepare Fluoxetine hydrochloride microcapsules by a modified solvent evaporation technique. The effect of sustained release of Fluoxetine hydrochloride from CAB microcapsules has been investigated via in-vitro dissolution test and has been compared to a commercial sustained release product (Prozac® capsules)

MATERIALS AND METHODS

Materials

- Fluoxetine hydrochloride (gift from Egyptian international pharmaceutical company (EIPICO), 10th of Ramadan, Egypt)
- Prozac®Weekly capsules (90 mg), Dista product Eli-Lilly Co. S.P.A. U.S.A.
- Cellulose Acetate Butyrate [9004-36-8], (Aldrich Chemical Co., Inc., Milwaukee, Wisconsin, USA).
- N-Hexane extrapure AR (Sisco Research Laboratories PVT. LTD., Mumbai- 400099- India)
- Magnesium Stearate, (NF, E.Merck, Darmestadt, Germany)
- Acetone, Light Paraffin Oil, Talc, Sucrose powder and Hydrochloric acid (El-nasr chemical company, Cairo, Egypt).
- Sorbitan monooleate (SPAN80), (Sigma Chemical Co., St. Louis., USA)
- Trisodium orthophosphate, (BDH chemicals, LTD., Poole, England).
- Methanol (Sisco Research Laboratories PVT. LTD., Mumbai- 400099- India)
- All other chemicals were of analytical grades and were used as received.

Equipment:

- Shimadzu double beam UV- visible spectro-photometer model UV- 1601PC connected to a promax computer fitted with UPVC personal spectroscopy software version 3.7 (Shimadzu Corporation, Kyoto, Japan).
- Dissolution Tester, six cups model TDD-6 (S.B.S. Instruments, Barcelona, Spain).
- Coating Pan, (model 300, working capacity 2 kg/time, speed of pot 42 rpm, pot diameter 300mm,weight 85 kg, dimensions 44×55×76 cm, Shang Hai HUAMAO, comerial and Industrial Co.)
- Air Pump, (model NS 111-50 cm^2 V230 Balma1, capacity 50 Lt., Balma, Italy).
- Spray painting gun (maximum supply pressure 4/8 bar, Italy)
- Mechanical stirrer(two blade, mLw, ER10,4cm diameter, made in GDR)
- Magnetic stirrer with hot plate (type NM4, 50 HZ, 220-240 volts, LAVAT, Czechoslovakia).
- Magnetic stirrer (Velp Scientifica, Italy).
- Sieves and mechanical shaker (type As200 basic, F. Kurt Retsch GmbH & Co.KG42781 Haan, Rheiniache Str.36., Germany)

Methods:

Construction of calibration curve of fluoxetine hydrochloride:

An accurately weighed amount of Fluoxetine hydrochloride was dissolved in methanol to obtain a stock solution with a concentration of 2500 ug/ml. aliquot (1 ml) was transferred to 100 ml volumetric flask, the volume was completed with distilled water, 0.1N HCl and phosphate buffer of pH 6.8 and mixed well to obtain a solution with a concentration of 25ug/ml. series of solutions containing different concentrations of Fluoxetine hydrochloride (1-10ug/ml) were prepared and the absorbance of each was measured at the maximum absorbance of Fluoxetine hydrochloride (227 nm) using either distilled water, 0.1 N HCl or phosphate buffer of pH6.8 as a blank [12].

Preparation of drug loaded spherical granules:

Sucrose granules of size 855 µm were used for drug loading using pan coating technique. Coating pan (angle of inclination 15^0) with the help of single baffle was used for preparation of spherical granules to improve the uniformity of tumbling action in the pan. Coating pan was preroughened with talc powder to prevent adhesion of sucrose granules to walls of it. Different drug to excipients ratios were prepared according to table (1). The Pan is heated to about 45^0C followed by the addition of sucrose granules. Light syrup (50% w/v) was sprayed intermittently with sprinkling of Fluoxetine hydrochloride- talc mixture till end of powder mixture and nearly spheronization of granules. The granules were then dried using the warm air then collected.

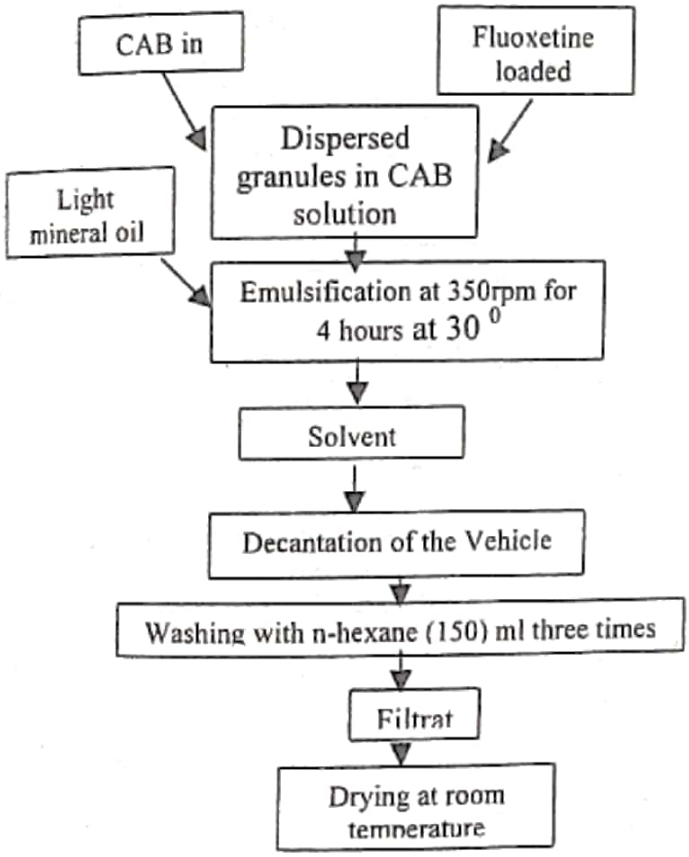
Table (1): The prepared fluoxetine hydrochloride formulations

Formulation No.	Uncoated granules prepared using the following Drug / excipients ratio	Microencapsulated granules prepared by using the following Coat/ core ratio
F-1	1:1	0.5:1
F-2	1:1	0.25:1
F-3	0.43: 1	0.5:1
F-4	0.33:1	0.25:1

Preparation of microcapsules:

Microencapsulated granules of Fluoxetine hydrochloride were prepared using a modified emulsion-solvent evaporation technique. Cellulose acetate butyrate (CAB) was used as the coating material. Preliminary experiments were carried out to determine the optimum conditions necessary for the preparation of microcapsules, including the effects of polymer concentrations, agitation speed, and temperature on the properties of microcapsules. The results revealed that 3.75% or 1.875% w/v of CAB were the optimum concentrations for the preparation of the microcapsules. Acetone was used as a solvent and light mineral oil as the external phase of the emulsion. Emulsification was carried out in a water jacketed beaker for 4 hours where temperature was kept at 30^0C during the process till complete removal of acetone. Emulsification was carried out using two-blade stirrer kept at 350rpm. One gram and half or 0.75 g of CAB was dissolved in 40 ml of acetone to produce 3.75% or1.875% w/v concentration. A polymer to granules ratio of 0.5:1 and 0.25:1 was used. Fluoxetine loaded spherical beads prepared by

coating pan were dispersed in the polymer solution with continuous stirring. This dispersion was emulsified into 100 ml of light mineral oil containing 1% and 0.5% w/v magnesium stearate and sorbitan monooleate respectively. The microcapsules were allowed to settle, and light mineral oil was decanted. The microcapsules were then thoroughly washed with 150 ml of n-hexane for three times to remove any oil residue. Microcapsules were then separated by filtration and allowed to dry overnight at room temperature. The emulsion solvent evaporation method used for the preparation of microcapsules of CAB and Fluoxetine hydrochloride is summarized in scheme 1.



Scheme 1: Microencapsulation of fluoxetine hydrochloride with CAB using modified emulsification solvent evaporation technique.

Determination of yield of the recovered microcapsules:

The dried microcapsules were weighed to determine the yield (%) of the recovered microcapsules using the following equation [18]:

$$\text{Yield\%} = \frac{\text{Weight of the collected microcapsules}}{\text{Total weight of core and polymer used}} \times 100$$

Sieve analysis of prepared microcapsules:

Individual batches were weighed and subjected to particle size analysis using a set of standard sieves having apertures of 300, 500, 710 and1000um. The microcapsules were placed on the topmost sieve and shaken by mechanical shaker at 240rpm for 15 min. the mean of three measurements for each sample was recorded. The mean particle size of microcapsules was calculated.

Drug loading of prepared microcapsules:

Microcapsules were crushed and powdered in a mortar. Accurately weighed 100 mg of this powder was extracted in 100 ml distilled water. The solution was then filtered; a sample of 10 ml was withdrawn, transferred to 100 ml volumetric flask, completed to volume with distilled water and assayed spectrophotometrically at 227 nm.

In-vitro drug release studies:

Drug release from different batches of microcapsules was carried out according to USPXXII paddle apparatus for delayed release (method A)*. The dissolution medium consisted of (750ml of 0.1 N hydrochloric acid); allowed to equilibrate to temperature of 37 ± 0.5^0 with stirring rate of 50 rpm. An accurately weighed sample of the microcapsules equivalent to 20 mg Fluoxetine hydrochloride was added to the dissolution medium. Five- ml samples were withdrawn through Millipore filter head at predetermined time intervals (0.5, 1, and 2 hrs) and replaced by an equivalent volume of the dissolution fluid preheated at the same temperature to maintain constant volume and temperature. **After 2 hrs, the medium was changed to the buffer stage by addition of 250 ml of 0.2M tribasic sodium phosphate that has been equilibrated to 37±0.5^0 to reach pH of 6.8. Sample withdrawal was completed as usual at predetermined time intervals 3, 4,5,6,7 and 8 hrs from zero time. The amount of drug released in case of acid stage or buffer stage was quantitated spectrophotometrically at 227 nm against the blank. The dissolution measurements were performed on triplicate samples from each batch.

*** Acid Stage**

**** Buffer Stage**

Kinetics of the drug release from microcapsules:

Release profiles of Fluoxetine hydrochloride was obtained by plotting the % released versus time showed a non-linear dissolution pattern, indicating that the release rate was not conforming to zero-order kinetics. In order to study the kinetics of drug release from the prepared microcapsules, the dissolution data were analyzed using several dissolution models including the Higuchi model[19].

RESULTS AND DISCUSSION

Construction of calibration curve of Fluoxetine hydrochloride:

Series of solutions of different concentrations of Fluoxetine hydrochloride ranging from 1 to 10 ug /ml in distilled water, 0.1 N HCl and buffer of pH6.8 were prepared. The absorbance values at 227nm of these solutions were recorded. The correlation between the absorbance values and corresponding concentrations are shown in table (2) and illustrated in fig. (1)

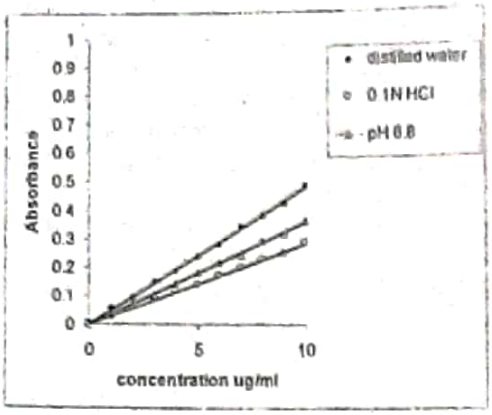


Fig (1): Standard calibration curves of fluoxetine hydrochloride in different solvent media.

Table (2); Characteristics of linear correlation between fluoxetine hydrochloride concentrations in various media and Its absorbencies.

Media used	Equation for standard curve	Correlation coefficient(r^2)
Distilled water	Y= 0.0479X	0.9987
0.1 N HCl	Y=0.0357X	0.9990
pH 6.8	Y=0.0281X	0.9996

Preliminary experiments:

Preliminary experiments were carried out to establish the optimum experimental conditions necessary for the preparation of the microencapsulated granules of Fluoxetine hydrochloride using cellulose acetate butyrate as a coating material. The optimum polymer concentrations were found to be 3.75 %w/v, and 1.875 % w/v. Higher polymeric concentrations were too viscous to emulsify and resulted in high and irregular microcapsules which settle down quickly, while at lower polymer concentration, microcapsules were unable to be formed. Magnesium stearate and sorbitan monooleate (span 80) were added to the external phase of the emulsion to help for the stability of the emulsion formed. Concentrations (> 1% w/v) of magnesium stearate, produced too viscous emulsion with the formation of aggregates of microcapsules, while lower concentrations (0.1, 0.25 %w/v) were insufficient to maintain the emulsion formed. Sorbitan monooleate, was used to provide an additional protective sheath around the polymer droplet and to prevent droplets from coalescence during the preparation of microcapsules. The temperature of the system was continually maintained at 30°C by using thermostatically controlled water bath. The stirring rate was maintained at 350rpm.

Recovery of the microcapsules:

The percentage yield (%w/w) of the microcapsules prepared by modified emulsion solvent evaporation technique was determined by dividing the total weight of the microcapsules obtained after filtration and drying by the total initial weight of the granules and polymer used. The % yield of the different microcapsules preparations varied from 77.78 to 98.67% for microencapsulated granules. The yield of microcapsules was increased by decreasing the coat/ core ratio from 0.5:1 or 0.25: 1. table (3).

Table (3): Characteristics of fluoxetine hydrochloride microcapsules prepared by emulsion solvent evaporation technique and cellulose acetate butyrate at different coat / core ratios

Formula no.	Uncoated granules with drug /Excipients ratio	Microencapsulated granules prepared at different coat /core ratios	Yield %	Theoretical drug content (%w/w)	Actual drug content (%w/w)
F-1	1:1	0.5:1	77.78	33.3	33.1
F-2	1:1	0.25:1	98.67	40	31.5
F-3	0.43:1	0.5:1	80	20	14.5
F-4	0.33:1	0.25:1	85.43	20	17.2

Size distribution of the microcapsules:

The size distribution of CAB microencapsulated granules of Fluoxetine hydrochloride was strongly affected by coat /core ratio of the dispersed phase. Increasing the proportion of the granules resulted in an increase in the mean diameter of the microcapsules as shown in figure (2) and table (4). Higher % frequency of large microcapsules (1000-710 um) was obtained as coat/ core ratio was decreased from 0.5: 1 to 0.25 1. It was found that formulas F2 and F4 (both are of 0.25 1 coat/ core ratio with different drug to excipients ratio) shown the highest frequency of particle size distribution.

Table (4): Sieve analysis Of fluoxetine hydrochloride microencapsulated granules prepared at different Coat/ core ratios

Microcapsules size range (um)	Mean diameter (um)	%Sieve fraction (frequency)			
		F-1	F-2	F-3	F-4
2000-1000 um	1500um	20	21.6	39	25
1000-710 um	855um	40	40.5	36.1	46.9
710-500 um	605 um	17.1	18.9	11.1	18.75
500-300um	400um	17.1	10.8	8.34	3.125
< 300um	300 um	5.8	8.2	5.46	6.225

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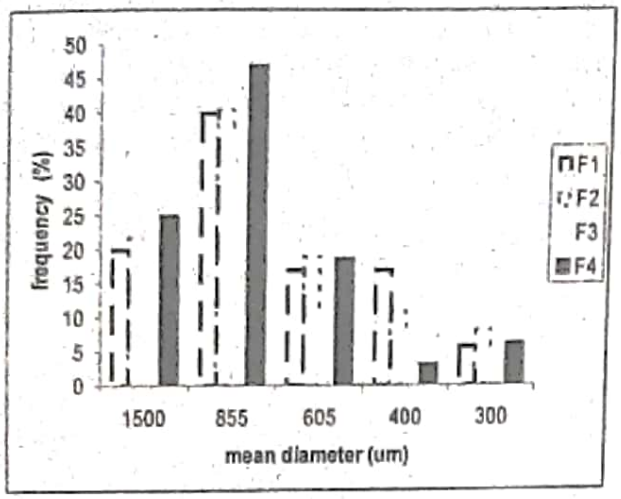

Fig (2): particle size distribution of fluoxetine hydrochloride microcapsules prepared with cab at different coat / core ratios.

In-Vitro drug release characteristics from microcapsules:

The dissolution rates of Fluoxetine hydrochloride from microencapsulated granules were studied and compared to that of Fluoxetine hydrochloride powder and uncoated granules. All the dissolution experiments were carried out using 0.1 N HCl for 2 hrs followed by buffer stage at pH6.8 for further 6 hrs. The drug release from the prepared microcapsules was strongly affected by the coat/core ratio, and pH of dissolution medium. The dissolution profile of Fluoxetine powder indicated that it dissolved rapidly within 5 min., while the dissolution profile of uncoated granules indicated that it dissolved with 50 min. it was found that for microcapsules prepared using cellulose acetate butyrate, the % drug released depended on pH. Figures (3-6) showed different drug release profiles from Fluoxetine hydrochloride microcapsules using CAB as a coating material.

Table (5): Effect of coat/core ratio on release of fluoxetine hydrochloride from its microencapsulated granules.

formula	% Drug released after the following time intervals in min.								
	30	60	120	180	240	300	360	420	480
Uncoated granules	82.36 ±1.150	96.56 ±0.665	99.7 ±0.404	100	100	100	100	100	100
Commercial sample	0.56 ±0.602	3.38 ±0.501	10.16 ±0.404	12.56 ±1.457	34.6 ±0.889	45.34 ±0.70	58.56 ±0.98	72.6 ±1.17	85.53 ±0.81
F-1	4.93 ±0.763	6.36 ±0.503	18.7 ±0.781	26.267 ±0.404	43.834 ±0.305	62.3 ±0.5	75.2 ±0.360	85.3 ±0.458	99.17 ±1.024
F-2	25.47 ±0.77	32.4 ±0.5	47.43 ±0.568	69.43 ±0.61	95.134 ±0.351	99.467 ±0.75	100	100	100
F-3	1.267 ±0.709	2.2 ±0.36	10.934 ±0.351	18.67 ±0.802	21.067 ±1.059	24.67 ±1.266	45.4 ±1.044	70.4 ±0.754	78.6 ±3.011
F-4	6.3234 ±0.390	21.34 ±0.550	24.867 ±0.251	31.34 ±0.802	45.567 ±0.611	56.293 ±1.122	73.34 ±1.069	99.2 ±0.754	99.867 ±0.230

*All values are mean ± S.D., n=3.

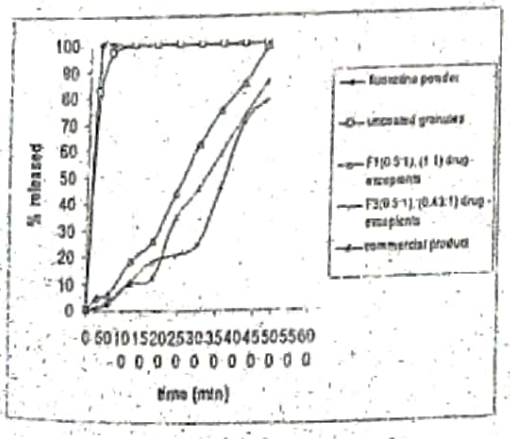

Fig (3): release profile of fluoxetine hydrochloride from the prepared microcapsules.

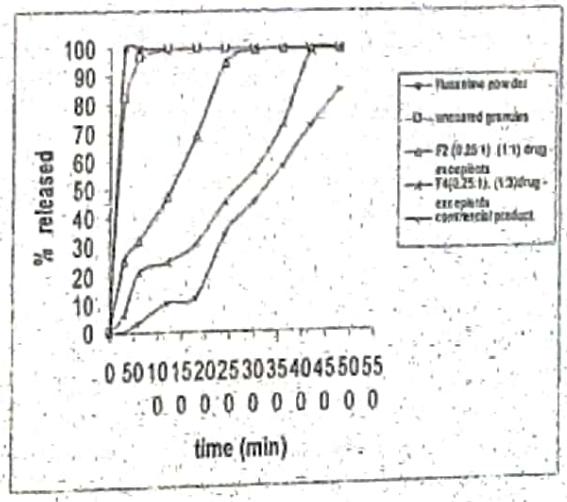

Fig (4): release profile of fluoxetine hydrochloride from the prepared microcapsules.

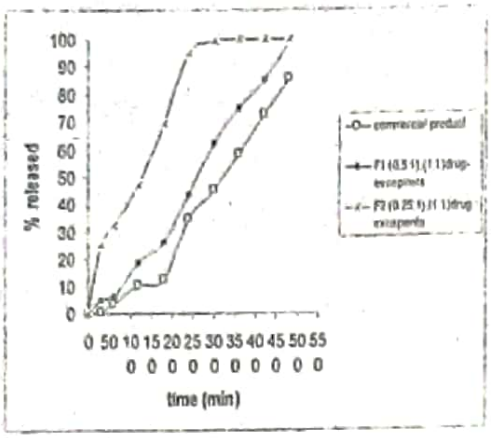

Fig (5): release profile of fluoxetine hydrochloride from the prepared microcapsules.

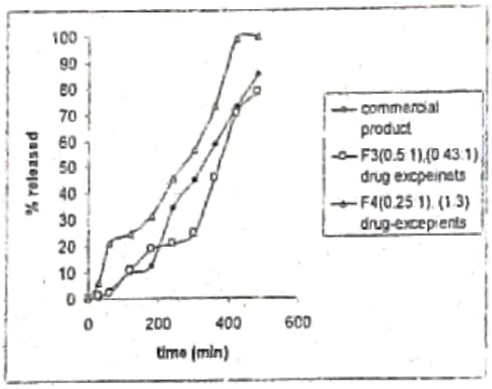

Fig (6): release profile of fluoxetine hydrochloride from the prepared microcapsules.

The release of Fluoxetine hydrochloride from the prepared microencapsulated granules by modified emulsion solvent evaporation technique was determined. It was found that release of Fluoxetine hydrochloride was more retarded from coated drug loaded granules from formulas F1 and F3. This was due to increase of diffusional path length[20]. Different coat/ core ratios were tested (0.5:1, and 0.25:1) and it was found that as coat/ core ratio increased, the release of Fluoxetine hydrochloride was reduced. Figures (3-6) showed different drug release profiles from microcapsules prepared by emulsion solvent evaporation technique using cellulose acetate butyrate as coating material. It was found that drug Excipients ratio affected drug release for the same coat/ core ratio. Figures (3,4) showed the effect of changing of drug excipients ratio on drug release for the same coat/ core ratio. As drug to excipients ratio decreased (F1& F3, F2 & F4) the release of Fluoxetine hydrochloride more retarded.

Relative dissolution rate (R.D.R):

The retardation of dissolution rate of Fluoxetine hydrochloride from the CAB microcapsules was estimated in comparison with the release rate of the drug from a commercial preparation (Prozac® microcapsules). The relative dissolution rate (R.D.R) was estimated (table 6) for CAB microcapsules. The relative dissolution rate was calculated by dividing the % drug released at specific times during the test (30, 60, 120, 180, 240, 300, 360, 420,and 480 min.) by that released from the commercial preparation (Prozac® microcapsules) mentioned above. Data for some preparations were less than 1 and for others were more than 1.Data less than 1 indicated high retardation efficiency of the microcapsules to the release of Fluoxetine hydrochloride. The effect of coat/ core ratio was the main factor in reduction of drug release. As coat/ core ratio increased, more retardation in release of drug was noticed. This could be due to increased diffusion path length by increasing the polymer concentrations. The relative dissolution rate values of F3 were less than 1 at (60, 240, 300, 360,420 and 480 min.). Table (6) indicated that formula F3 was superior in retarding drug release.

Table (6): effect of polymer to drug ratio on dissolution rate of fluoxetine hydrochloride microcapsules prepared with cab.

Formula code	R.D.R after time (t, min)*								
	30	60	120	180	240	300	360	420	480
F1	8.7	1.8	1.8	2.08	1.2	1.3	1.2	1.1	1.1
F2	44.9	9.58	4.6	5.5	2.7	2.1	1.7	1.3	1.16
F3	2.2	0.65	1.07	1.48	0.6	0.54	0.77	0.9	0.91
F4	11.1	6.31	2.4	2.4	1.3	1.2	1.2	1.3	1.16

* Relative dissolution rate

Drug release kinetics from CAB microcapsules:

In view of dissolution profile of Fluoxetine hydrochloride from microencapsulated granules and due to the fact that microcapsules retained their shape and size even after 8 hours of dissolution time, the release of drug appeared to be primarily governed by diffusion –leaching process of the drug molecules through capillary channels formed in the polymer matrix. The curved shape of release profile of Fluoxetine hydrochloride indicated that it is not a zero order release pattern, the Higuchi model was used to analyze the dissolution data to be certain that release of Fluoxetine hydrochloride is diffusion controlled with limited dissolution.

The Higuchi model is expressed according to following equation:

$$F = K_2 t^{1/2}$$

Where F represents the fraction of drug released in time t and K_2 is the Higuchi dissolution constant[21].

Figures (7-10) show the plots of the dissolution data using this equation to study the release of Fluoxetine hydrochloride in different coat/ core ratios prepared by modified emulsion solvent evaporation technique. The results showed that the drug release was affected by coat/ core ratio as indicated by change

in the slopes of dissolution plots. The release of drug was increased by increasing the slope (table 7).

Table (7): effect of coat/core ratio on the slope and correlation coefficient of the dissolution lines (higuchi equation for dissolution) of fluoxetine hydrochloride microencapsulated granules

Formulation no.	Slope	Correlation coefficient (r^2)
Prozac® capsules	4.076	0.8242
F1	4.803	0.8818
F2	5.196	0.9477
F3	3.471	0.7526
F4	4.740	0.8822

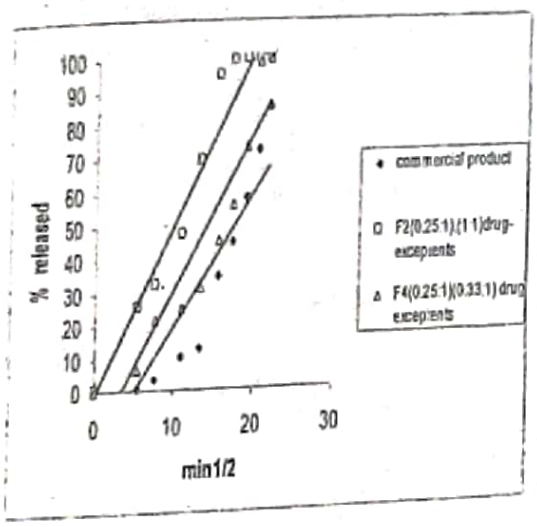

Fig (7): higuchi plot of fluoxetine hydrochloride release from the microencapsulated granules.

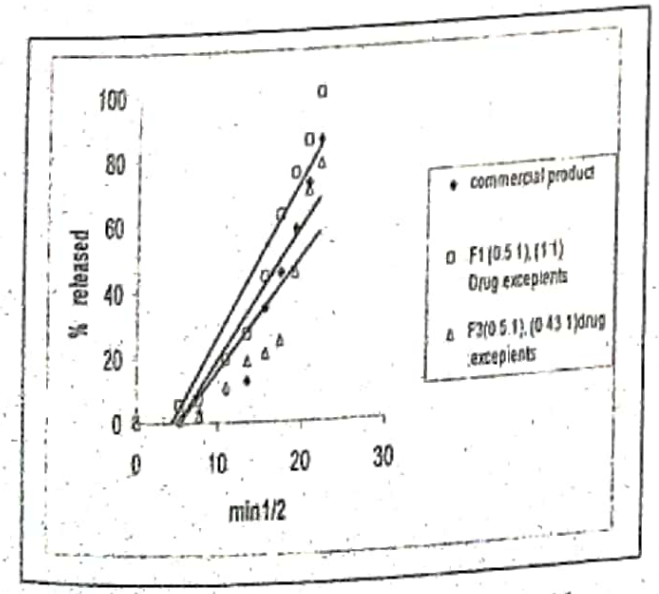

Fig. (8): higuchi plot of fluoxetine hydrochloride release from the microencapsulated granules.

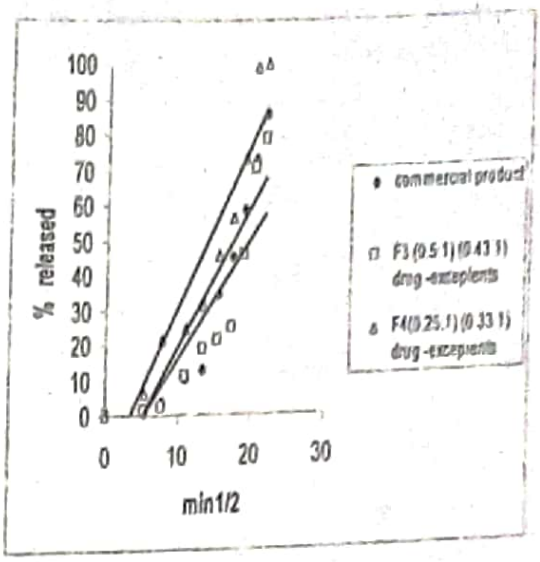

Fig. (9): higuchi plot of fluoxetine hydrochloride release from the microencapsulated granules.

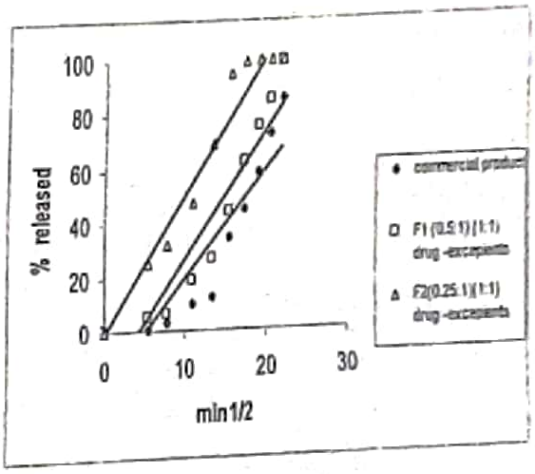

Fig. (10): higuchi plot of fluoxetine hydrochloride release from the microencapsulated granules.

3.8. Relative T_{50} :

The relative T_{50} dissolution time of the prepared microencapsulated granules was calculated by dividing the T_{50} dissolution time of the prepared microcapsules by the T_{50} dissolution time of commercial product (table 8). A higher relative T_{50} means a more sustained drug release relative to the commercial microcapsules. For the prepared microcapsules, it was found that the relative T_{50} was dependant on coat/ core ratio as well as on drug to excipients ratio of granules themselves (table 8). The relative T_{50} was 0.738 and 1.064 for F1 and F3 that means that F3 is more sustained than commercial microcapsules. Formula 1 and formula3 were prepared by the same coat/ core ratio but with different drug to excipients ratio. For F2 and F4, T_{50} was 0.414 and 0.791 respectively. This means that release of Fluoxetine from them is higher than that of commercial microcapsules[20].

Table (8): release characteristics of prepared fluoxetine hydrochloride microencapsulated granules compared to the commercial product using $T_{50\%}$ As the Comparison Parameter.

Formulation code	Coat/ core ratio	Drug to excipients ratio	$T_{50\%}$ (min)	Relative $T_{50\%}$*
F1	0.5:1	1:1	262	0.738
F2	0.25:1	1:1	147	0.414
F3	0.5:1	0.43:1	378	1.064
F4	0.25:1	0.33:1	281	0.791

*Relative dissolution ($T_{50\%}$) = dissolution ($T_{50\%}$) of the prepared microcapsules divided by the dissolution ($T_{50\%}$) of commercial microcapsules (prozac® capsules).

CONCLUSIONS

1. Discrete, free flowing microencapsulated granules of Fluoxetine hydrochloride were prepared by two methods namely pan coating and modified emulsion solvent evaporation technique.
2. The release rates of Fluoxetine hydrochloride from these microcapsules were considerably sustained as compared to those of a commercial sustained – release formulation (Prozac® capsules).
3. Different coat/ core ratios were prepared by modified emulsion solvent evaporation technique using cellulose acetate butyrate as the coating material.
4. The retardation of the release rate was dependant on the coat/ core ratio, drug to excipients ratio and pH of dissolution media.
5. The release rate profiles obeyed the diffusion controlled mechanism of Higuchi model.

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تحضير وتقييم حويصلات ممتدة المفعول لهيدروكلوريد الفلوكستين

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تم تحضير حبيبات تحتوى على نسب مختلفة من العقار و تحويلها إلى الشكل الكروي باستخدام حلة الكسوة ، ثم استخدمت طريقة تبخير الوسط المنتشر للمستحلب باستخدام بيوترات خلات السليلوز كمادة مغلفة بنسب ٢٠,٠ ، ٣٣,٣% لحوصلة هذه الحبيبات.

وقد وجد أن المحتوى الدوائي للحويصلات يتأثر بنسبة تركيز المواد المغلفة حيث يزداد المحتوى الدوائي للحويصلات بتقليل نسبة المادة المغلفة.

كما أوضحت دراسة معدل انطلاق العقار من الحويصلات في المحاليل المشابهة للوسط المعوي (الرقم الهيدروجيني ٦,٨) وجد أنها تتأثر بنسبة المواد المغلفة ، المحتوى الدوائي للحويصلات .

كما لوحظ نقص معدل انطلاق هيدروكلوريد الفلوكستين بزيادة نسبة المواد المغلفة، بالإضافة إلى نقص معدل الانطلاق من الحويصلات عند مقارنتها بالحبيبات الغير مغلفة.

كذلك لوحظ نقص معدل الانطلاق مع خفض الأس الهيدروجيني لوسط الانطلاق حيث يكاد ينعدم تماما في الوسط المعدي.

كذلك لوحظ نقص معدل الانطلاق من الحويصلات عند مقارنته بهيدروكلوريد الفلوكستين الغي لمحو صل أو مقارنته بالمستحضر التجاري محل الدراسة.