UNDER PEER

In-Vitro and *In-Vivo* Relationship of gabapentin from Floating and Immediate Release Tablets

Abstract:

Gabapentin is effective against post-traumatic spinal injury-induced neuropathic pain. It requires high dosage and frequency in the management of neuropathic pain. The present research work was an attempt to formulate and evaluate gabapentin gastro-retentive tablets to prolong gastric residence and increase drug absorption and further increase bioavailability. The floating tablets of gabapentin were prepared in two doses (300 and 600 mg) by using two polymers (hydroxyl propyl methyl cellulose and hydroxyl propyl cellulose). Immediate release tablets of gabapentin containing the same doses were prepared and used as reference formulations. The physicochemical characteristics of the prepared tablets were determined (drug content, weight variation, friability, hardness, thickness and diameter). Drug release from the prepared tablets was followed and found that by increasing drug concentration in the tablets release rate increases. Floating tablets showed prolonged drug release (over 96%) to more than 15 hrs. Immediate release tablets showed over 97% drug release within 48 min. In-vivo results showed that plasma exposure to gabapentin in animals receiving the drug does not dose proportional and therefore may not reach therapeutically useful levels. AUC_{0-24} and C_{max} in case of 300 mg tablets are more than those in case of

600 mg tablets. The *in-vivo* release of gabapentin does not correlate with the *in-vitro* release of the drug.

Keywords: Gabapentin, Floating Tablets, Sustained release tablets, Pharmacokinetics

Introduction

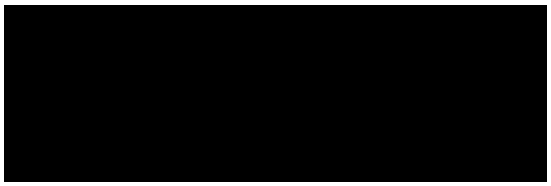
For a large number of drugs, transport across the intestinal epithelium in each segment of GIT is not uniform and often limited to a particular segment (window) only **(1)**. The oral controlled release delivery becomes more difficult due to the inability to restrain and localize the drug delivery system within the desired region of the GIT. The concept of regulatory drug delivery in the human body has been existence for many years because of major benefits such as improved patient compliance and decreased side effects.

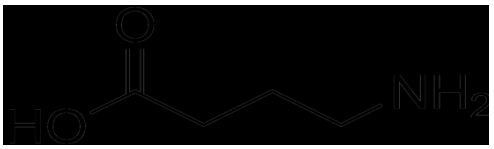
Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceeds save therapeutic levels quickly or fall below the minimum effective level **(2)**.

Numerous oral controlled release drug delivery systems have been developed to prolong drug release. An important prerequisite for successful performance for an oral controlled release drug delivery system is that the drug should have good absorption throughout the whole GIT in order to ensure continuous absorption of released drug **(3)**.

Gabapentin [1- (aminomethyl) cyclohexane acetic acid] is a structural analogue of ɤ- amino-butyric acid (GABA)

with an incorporated cyclo hexyl ring Fig 1.





Gabapentin ɣ- amino-butyric acid (GABA)

Fig.1: Chemical structure of gabapentin and ɣ- amino-butyric acid

Gabapentin is a white to off-white crystalline solid and currently marketed as aadjunctive therapy for partial seizures in an adult with epilepsy and for the management of postherpetic neuralgia **(4)**. The drug is used in the of amyotrophic lateral sclerosis, painful neuropathic, hot flashes (cancer and/or postmenopausal- related), fibromyalgia, neuralgia, neuropathy, chronic pain, prevention of migraine, with minimal side effect profile when compared with other drugs **(5, 6)**.

The medications traditionally used for neuropathic pain include opioid analgesics, non-steroidal anti-inflammatory drugs and tricyclic antidepressants. The use of these antidepressants is limited by unwanted side effects and risk of cardiovascular mortality **(7- 9)**.

For treating the peripheral and neuropathic pain caused by traumatic spinal injuries, gabapentin is used up to 3.6 g/day in tablet, capsule and oral solution **(10, 11)**.

Gabapentin is freely soluble in water (4491mg/l at 25^{o}C), basic and acidic aqueous solutions with dissociation constants pk_a of 3.68 and 10.7, respectively. The absolute bioavailability of approximately 50% makes gabapentin a good candidate for improvement of its oral bioavailability **(12)**. Due to the short half-life of gabapentin (5-7 h) frequent dosing (at least three times daily) is required for maintaining the desired drug level for the whole day. But this leads to significant fluctuations in the plasma concentration of gabapentin **(13, 14)**.

Gabapentin is associated with the absorption window phenomenon because it is absorbed through a large neutral amino acid transporter (with limited transport capacity) located in the upper small intestine **(15, 16)**.

Prolonged stable exposure to gabapentin may provide other clinical benefits; including greater efficacy prolonged duration of action as well as a reduced incidence of adverse effects related to peak drug levels. However, it has been difficult to achieve these benefits with a sustained release formulation of gabapentin, primarily due to the lack of significant absorption in the large intestine **(17, 18)**.

Due to limited capacity nature of transporter, the higher doses of gabapentin cannot give the higher plasma levels therefore to overcome the above limitations; the floating drug delivery system (FDDS) of gabapentin have been investigated to increase the gastric residence and hence, the increased drug delivery in its absorption window.

In this study, floating tablets containing gabapentin 300mg (F_1) and 600mg (F_2) were prepared using hydroxyl propyl methyl cellulose (HPMC) as well as hydroxyl propyl cellulose (HPC) in order to improve the drug release with prolonged drug delivery. The prepared tablets were evaluated for *in-vitro* and *in-vivo* activity.

Materials and methods:

Gabapentin was obtained from Sigma- Aldrich, (St. Louis, Mo, USA), HPMC k15 and HPC were obtained from Shinyo Puse Chemicals Co., Japan, Magnesium stearate and Aerosil were obtained from S D Fine Chem.

Mumbai. Deionized water was purified using Milli-Q system (Millipore, Modified. MA, USA). Potassium dihydrogen phosphate and sodium hydroxide were of analytical grade. Other excipients were of reagent grades.

Preparation of gabapentin floating tablets:

Gabapentin floating tablets were prepared to adoptg wet granulation technique. Table 1 shows the composition of the proposed gabapentin floating tablets (F_1 and F_2). Table 2 shows the composition of gabapentin immediate release tablets.

Table 1: Composition of gabapentin floating tablets

Martial Name	Quantity mg/ tablet	
	F_1	F_2
Active Ingredient		
• Gabapentin	300	600
Inactive Ingredient		
• Hydroxyl propyl methyl cellulose (K_{15})	160	320
• Hydroxyl propyl cellulose (EF)	30	60
• Aerosil 200	5	10
• Magnesium stearate	5	10
Coat		
• Hydroxyl propyl methyl cellulose (ES)	8.5	17
• Polyethylene glycol 6000	2	4
• Titanium oxide	1.5	3
• Talc	0.5	1

Preparation of gabapentin immediate release tablets:

Tablet 2 shows the composition of the proposed immediate release gabapentin tablets (F_3 and F_4)

Table 2: Composition of gabapentin immediate release tablets

Martial Name	Quantity mg/ tablet	
	F_3	F_4
Active Ingredient		
• Gabapentin	300	600
Inactive Ingredient		
• Maize starch	30	60
• Crospovidone	30	60
• Microcrystalline cellulose (KG-1000)	69	138
• Microcrystalline cellulose (pH 102)	165	330
• Magnesium stearate	6	12
Coat		
• Hydroxyl propyl methyl cellulose (ES)	10.8	21.6
• Polyethylene glycol 6000	3.6	7.2
• Titanium oxide	1.8	3.6
• Talc	1.8	3.6

The utilized wet granulation technique using a water-ethanol mixture (1:1) was as follows: a solution was prepared to contain HPMC (K_{15}), HPC (EF) and aerosil which were added to gabapentin bulk powder to improve its poor compressibility. After kneading, it was sieved to form granules (60 mesh sieve, 0.425 mm diameter) and then dried to 3% moisture content (SHIMADZU Moisture Balance, Moc 120H, T-Rl-015). The granules were sieved

again and mixed carefully with the required quantity of magnesium stearate and the final blend was mixed thoroughly for 5 min and compressed into tablets of the average weight of 470 and 940 mg. Coating of the prepared tablets was then done by the method adopted by leon Lashman et al **(19)**. The weights of the coated tablets were

482 and 965 mg respectively.

Infrared spectroscopy (FTIR)

A qualitative IR been performed for pure gabapentin, gabapentin with HPMC (K15) and gabapentin with HPC (EF). Samples of 2-3 mg were ground and mixed with potassium bromide (IR grade), compressed into disks in the compressor unit under vacuum at a pressure of 10 ton/cm^2 and scanned from

4000 cm^{-1} to 400 cm^{-1} with an empty pellet holder acting as a reference using FTIR analyzer (Perkin Elmer model).

FT-IR studies were carried out to check for any interaction between the drug and the polymer. Chemical integrity of the drug was determined by comparing the IR spectra of the drug and drug coated with the chosen polymer.

X-ray Diffractometry (XRD)

X-ray Diffractometry of gabapentin granules weas performed by a diffractometer using model (Joel JDX-8030, Japan) equipped with a graphite crystal monochromator (Cu-Kα) radiations to observe the physical state of drug in the granules.

Drug Content:

Ten tablets were powdered in a mortar (either containing 300 mg or 600 mg gabapentin (F_1, F_2, F_3 & F_4) respectively. Weight accurately, a quantity equivalent to 100 mg of gabapentin was transferred to a 100 ml volumetric flask containing 10 ml of phosphate buffer with pH of 6.8. Flask was shaken for some time and made up the volume up to 100 ml with the buffer. Tem ml of primary stock solution were taken into another volumetric flask and made up to volume with buffer. The absorbance was measured spectrophotometrically at 210 nm using the buffer as a blank **(19)**.

Weight Variation:

Twenty tablets were randomly selected and weighed individually and together in a single pan balance (capacity 311g and sensitivity 0.01g). The average weight was noted and the standard deviation was calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablets differs by more than double percentage limit **(20)**.

$$\% \text{ Deviation} = (W_{avg} - W_{initial}) / W_{avg} \times 100$$

Where Wavg : average weight of tablets, Winitial: individual weight of tablet.

Friability:

Roch Friabilator (Agilent Technologies USA) was utilized in order to test the strength of the tablets. Friability is expressed in percentage (%). Ten tablets were initially weighed (W_o) and put into the apparatus **(21, 22)**. The Friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by:

$$\% \text{ Friability} = W_o - W / W_o \times 100$$

Where W_o: initial weight of tablets, W: final weight of tablets

% friability of tablets less than 1% are considered acceptable.

Hardness:

Hardness reflects the ability of a tablet to withstand mechanical shocks while handling. It is tested by utilizing Monsanto hardness tester (Aglient Technologies, USA). The value is expressed in $kg.cm^{-2}$. Ten tablets were randomly chosen and the hardness of the tablets wreas determined **(23)**.

Thickness and diameter:

Physical dimensions of the tablet such as thickness and diameter are essential for consumer acceptance and tablet uniformity. Thickness and diameter of the tablets were measured using Vernier Callipers. It is expressed in mm. Five tablets were used and the average values were calculated **(24)**. Limits of variation must not exceed ± 5% of the standard.

***In-vitro* drug release study:**

The drug release profiles from the tablets were studied using USP dissolution test apparatus employing paddle type (Type II, Paddle type, Copley, England). The rotation of paddle was fixed at 50 rpm and the temperature of 37±0.5^{o}C was maintained throughout the experiment. The dissolution medium was 900 ml phosphate buffer solution (pH 6.8). Samples of 5 ml were withdrawn at predetermined time intervals and were replaced with the same volume of fresh dissolution at the same temperature. Aliquots were removed, filtered through 0.45mm membrane filter and assayed for gabapentin utilizing double beam UV-Visible spectrophotometer at 210 nm. Each dissolution test was repeated 3 times and the mean values with standard deviations were presented.

***In-Vivo* study:**

Healthy male Wistar rats (300-350 g) were used for the study and were obtained from national researches centre (Cairo, Egypt). The rats were kept in standard environmental conditions of light and temperature. The rats were allowed free access to drinking water and standard diet; Rats were used after a resting period of 2 days post procurement. In-vivo experimental protocols had the approval of the institutional animal ethics committee (IAEC) (IAEC/PROPOSAL/DB-4/2010). Four rats were used under fasted conditions for 18 hrs. in each experiment (Four experiments, F_1, F_2, F_3 & F_4). One tablet corresponding to either 600 mg or 3oo mg drug in the sustained release or immediate release formulation was administered orally to the animals with a washout period at least 1 week between two consecutive administrations. Serial blood samples (1.5 ml each) were collected from the ear vein in a pa tt predetermined time intervals extending to 36 h. Plasma was immediately obtained by centrifuging blood samples at 3000 rpm for 10 min. All samples were stored frozen at -20^{o}C until analysis. Plasma levels of gabapentin were assayed by HPLC.

Analysis of gabapentin in rat plasma:

The HPLC system (Zorbax Eclipse XDBC-8, 250× 4.60 mm, 5 µ, 40^{o}C), mobile phase is composed of acetonitrile, methanol, buffer (3.0) (7: 36: 57) %. The detector is set at 210 nm with a flow rate of 0.95 ml/min. A portion of the sample (50 µl) was injected into the column.

Calculation of pharmacokinetic parameters

The pharmacokinetic parameters were calculated through a weighted least-squares procedure, with the aid of the non-linear regression programs, SigmaPlot ver. 8.0(SPSS Inc., Chicago, IL, U.S.A.) and Micromath Scientist® (Micromath®, Saint Louis, MO, U.S.A.). Plasma drug concentrations for 24 h were used to calculate

pharmacokinetic parameters because plasma drug concentrations at 48 h were less than the limit of quantitation. AUC_{0-24} is the area under the plasma concentration versus time curve, calculated using the trapezoidal rule for the time interval 0 to the last measurable point, 24 h. Elimination half-life, $t_{1/2}$ was calculated as follows: $t_{1/2}$ =

0.693/ke. The peak plasma concentration (C_{max}) and time to reach the maximum drug plasma concentration (T_{max}) were determined from visual inspection of the concentration-time plots.

Statistical Analysis:

One way ANOVA test followed by Tukey posttest was used for comparisons between the treatment and control groups. Data were presented as Mean ± SD. The P values <0.05 was considered as significance level during this study.

Results and discussion:

Infrared spectral analysis:

Infrared studies (Figures 2a, 2b, and 2c) revealed that there is no neither appearance of new peaks nor disappearance of existing peaks, which indicated that there is no interaction between the drug and the polymers used.

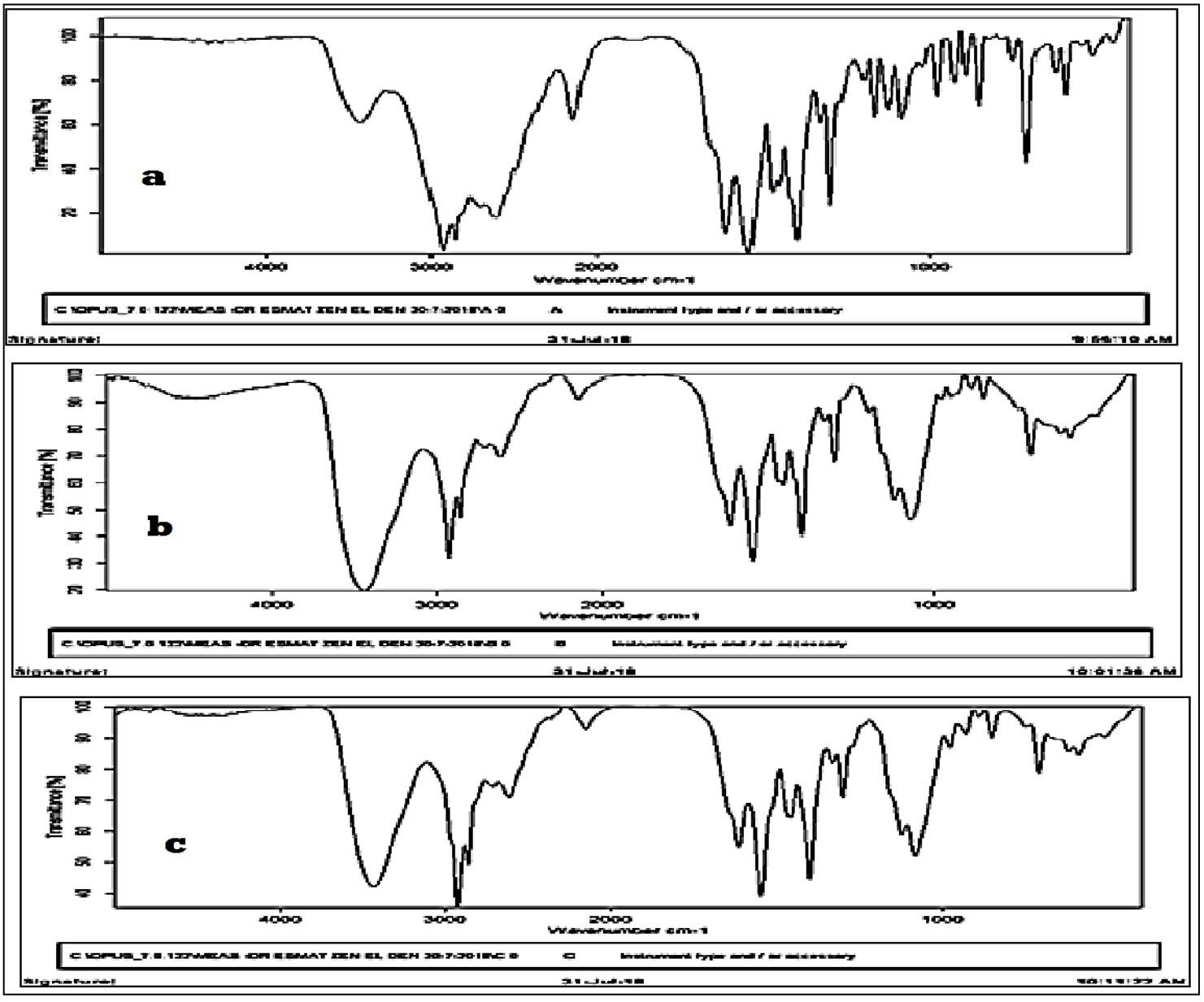


Figure 2: IR spectra of gabapentin free drug (a), gabapentin with HPMC (b), gabapentin with HPC(c)

The IR the usual -NH stretching regions (3500-3300 cm^{-1}). However, an IR band absorption in the region of 3200-2800 cm^{-1} was observed, which was due to the $-NH_3^+$. The broad peak at 3300 cm^{-1} for gabapentin might be attributed to the stretching vibrational modes of hydroxyl groups of water molecules in the gabapentin hydrate. The peaks near at 2123-2200 cm^{-1} corresponded to the distinct side chain and/or CN stretching vibration of all gabapentin. In the region of 1700-1500 cm^{-1}, the IR bands could be assigned as the ionized asymmetric carboxylate and NH_3^+ deformation vibration, respectively. From 1500 to 1350 cm^{-1}, these bands corresponded also to the asymmetric carboxylate band and/or CH_2 deformation band. Below
1350 cm^{-1}, these peaks might be used as a fingerprint of gabapentin.

IR studies show no interaction between drug and excipients. Additional peaks were absorbed in granules which could be due to the presence of polymers and indicated that there was no chemical interaction between gabapentin and other excipients. The spectra showed no incompatibility between the polymers and gabapentin. The spectra of the polymers and the free drug are given in the figures (2-a, 2-b and 2-c).

X-ray diffractometry (XRD):

In order to confirm the physical state of the drug in the microspheres, powder X-ray diffraction studies of the drug alone and drug loaded microspheres were carried out(Fig. 3-a, 3-b and 3-c).

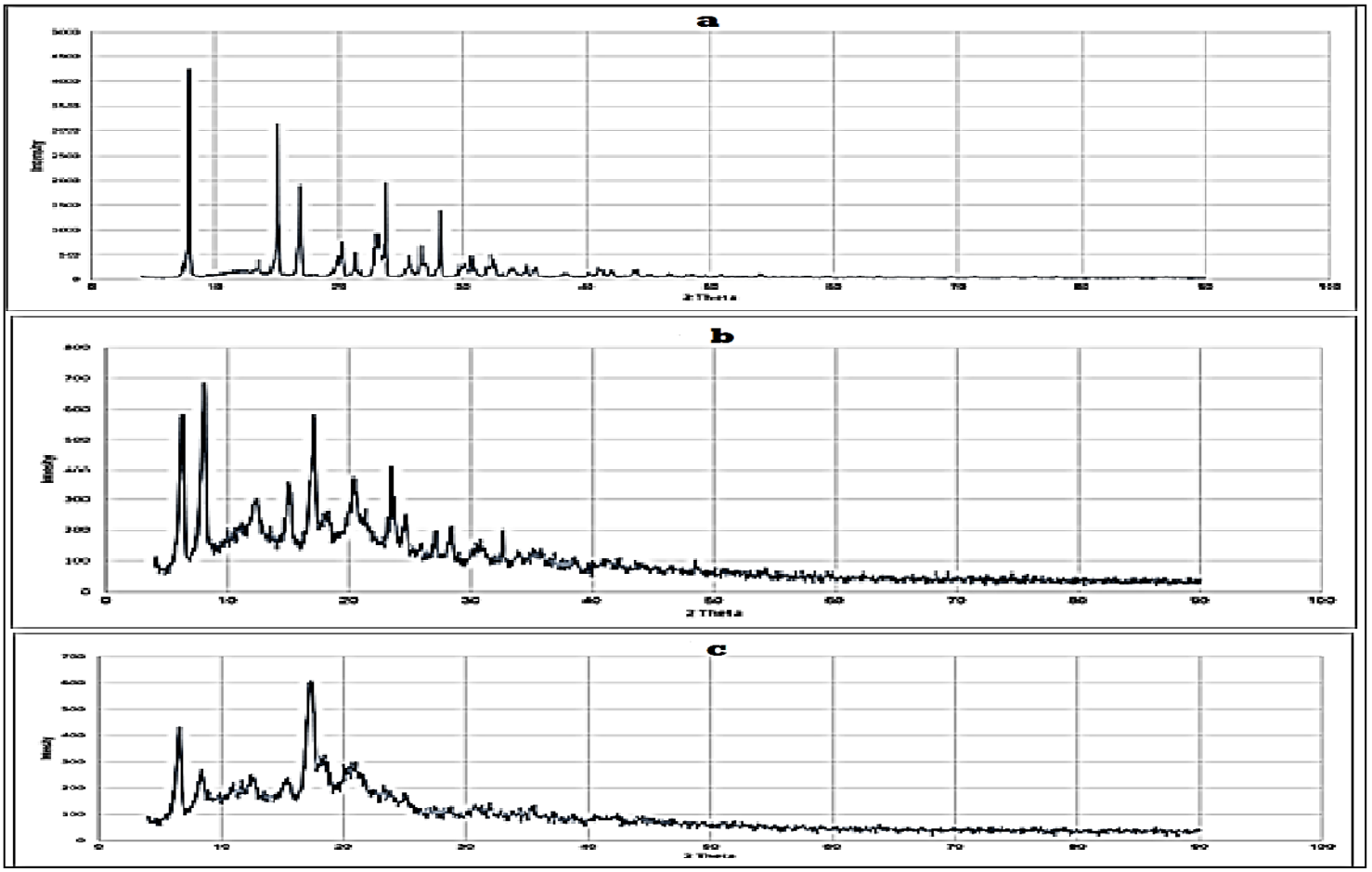


Figure 3: X-ray diffraction of gabapentin free drug (a), gabapentin with HPMC (b), gabapentin with HPC(c)

X-ray diffractograms of the samples showed that the drug is completely amorphous inside the granules. This may be due to the conditions used to prepare the granules which lead to complete drug amorphization.

Table 3 shows the various post-compression parameters drug content, weight variation, friability, hardness, thickness and diameter.

Table 3: Quality control tests of the prepared tablets

Formulation code	Drug content (%)	Weight variation (mg)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)
F_1	100.22 ± 0.13	510 ± 2.3	0.042 ± 0.01	8.60 ± 0.40	8.50 ± 1.2	16.50 ± 1.1
F_2	99.98 ± 0.26	1003 ± 4.8	0.053 ± 0.03	8.90 ± 0.30	9.20 ± 1.1	20.10 ± 2.1
F_3	99.79 ± 0.12	620 ± 2.9	0.036 ± 0.01	8.40 ± 0.21	8.20 ± 1.3	15.20 ± 1.2
F_4	99.28 ± 0.90	1230 ± 6.2	0.048 ± 0.03	9.30 ± 0.33	9.30 ± 1.6	22.10 ± 1.3

From table 3, all post compression parameters (drug content, weight variation, friability hardness, thickness, diameter as well as tablet parameters) are in the required limits.

***In-vitro* release characteristics:**

The *in-vitro* release profiles of gabapentin from both types of tablets (sustained & immediate release) in the dissolution media (6.8 buffer solution) reis presented in Figure 4.

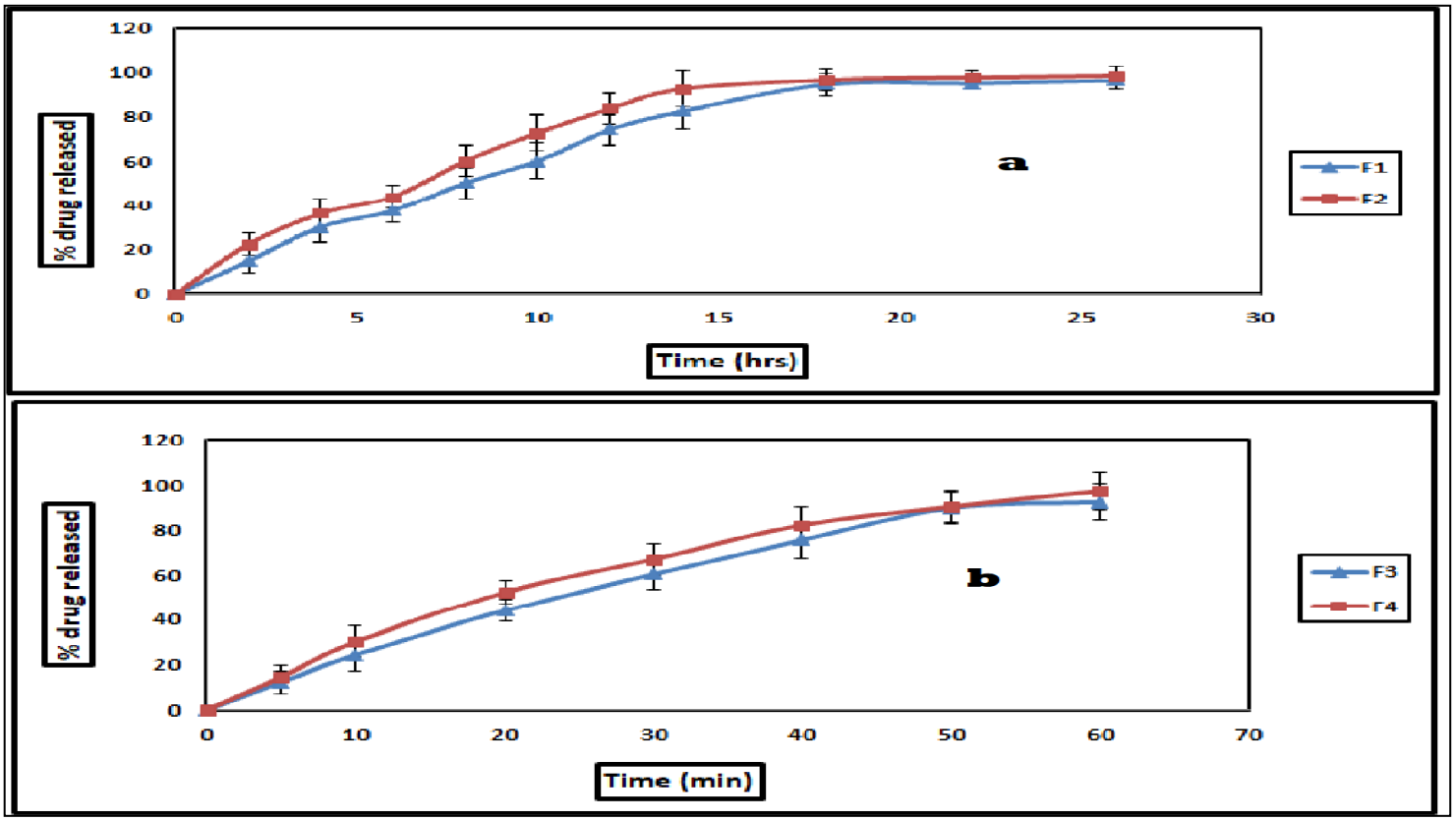


Fig 4: Release profile of gabapentin a: from sustained-release tablets, b: from immediate release tablets

Gabapentin was quickly released from the immediate release tablets after a short lag time (3.2- 5.6 min), whereas the mean lag time of the sustained release tablets was relatively delayed (12.8- 20.1 min). Within about 30 min, 60- 70 % of the drug was released from the intermediate release tablets in the dissolution media. The film coating did not prevent the immediate release tablets from quickly releasing the drug in the dissolution medium. Dissolution profiles of gabapentin from immediate release tablets indicated that the drug was quickly dissolved after the disintegration of tablets in the dissolution medium. The sustained release tablets become swollen rather

than

eroding or disintegrating during the experiment, and remained in the dissolution medium until the end of the experiment. The presence of high concentration of polymer (hydroxyl propyl methyl cellulose K_{15} and hydroxyl propyl cellulose EF 38%) of the tablet weight was the cause of increasing the swelling index, and retarding drug release from the tablets. Swelling of the sustained release tablets is considered due to the excellent swelling capacity of hydroxyl propyl methyl cellulose as well as its effect on increasing the medium viscosity. Hydroxyl propyl methyl cellulose has a great role in enhancing tablet floating in the stomach, an effect which increases the residence time of the drug in the GIT enhancing the sustained drug effect **(25)**.

Presence of polymer controls the release of the drug. When a hydrophilic polymer is exposed to aqueous media it undergoes rapid hydration and chain relaxation to form a viscous gelatinous layer (gel layer). The rate of diffusion out of the gel layer and the rate of tablet erosion control the overall dissolution rate and delivery of the drug **(26)**. The overall drug release is affected by the rate of water uptake as well as the diffusion rate of the drug through the swollen gel. High polymer content results in greater amount of gel being formed. The formed gel increases the diffusion path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug. As a result, a reduction in drug release rate is obtained **(27, 28)**. Seok Rhee *et al* **(29)** and Peng-Ju *et al* **(30)** reported that the dissolution rate for sustained release tablets containing gabapentin are unaffected by pH. Gabapentin is amphoteric in nature and has two pk_a's, 3.7 and 10.7 due to the carboxylic acid group and the primary amine group respectively. The drug predominantly exists as cation at acidic pH, and an anion at basic pH and has a zwitterion at intermediate values of pH between two pk_a values.

***In-vivo* release study:**

Plasma drug concentration vs. time profiles after oral administration of gabapentin in the sustained release as well as immediate-release tablets are shown in fig. 5.

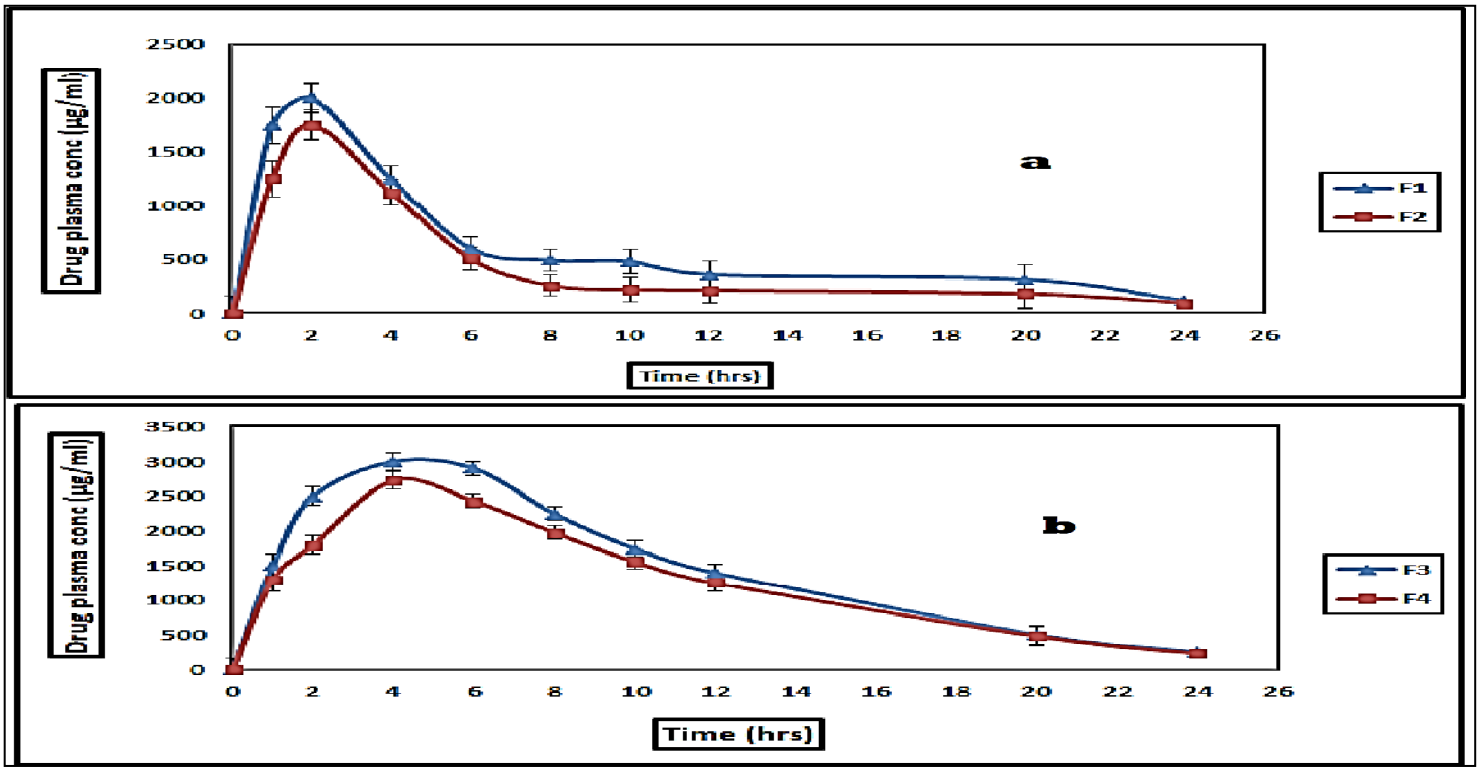


Fig. 5: Plasma concentration of gabapentin after oral administration of sustained-release tablets (a) and immediate release tablets (b)

From the obtained results, it is obvious that large doses (600 mg) showed less bioavailability than small doses. *In-vivo* release of gabapentin did not correlate with the *in-vitro* release of the drug. Gabapentin has a narrow absorption widow as seen with metformin **(31, 32)** and levodopa **(33, 34)**. Metformin was found to have lower bioavailability than conventional immediate-release tablets **(35, 36)**. Gabapentin is mainly absorbed into the upper gastrointestinal tract **(17)**. The sustained release tablets could not easily pass through the partially constructed sphincter due to the original size of the sustained release tablets and may remain in the stomach for more than 3h especially if containing a gastroretentive agent. These results are coincided with the time to reach the maximum concentration (T_{max}) which was obtained from gabapentin sustained-release tablets. Several researchers highlight the formulation and Evaluation of Ketorolac Tromethamine-loaded Albumin microspheres for Potential Intramuscular Administration (**36-40).**

Pharmacokinetic parameters of gabapentin after oral administration of immediate as well as sustained release doses to rats under fasted condition are shown in table 4.

Table 4: Pharmacokinetic parameters of gabapentin after oral administration to rats

Parameters	Sustained release tablets		Immediate release tablets	
	F_1	F_2	F_3	F_4
AUC (µg. hr/ml)	497.12±5.23	398.08±2.89	326.65±6.77	298.39±9.56
C_{max} (µg/ml)	37.59±1.65	35.31±1.23	43.88±.37	40.09±0.76
T_{max} (h)	2.00±0.21	2.50±0.12	1.40±0.74	2.10±0.23
$T_{1/2}$ (h)	5.69±0.53	4.17±0.90	4.36±0.44	3.22±0.71

(Mean ± S.E., n = 3)

Controlled release systems like floating tablets show various advantages over the single unit dosage form tablets. These systems are devoid of any adverse effects like dose dumping which is a quit common adverse effect compared to the conventional release dosage form.

Although the floating tablets did not disintegrate and had slow drug release characteristics, it showed similar pharmacokinetics parameters to the immediate release tablets, which rapidly disintegrated & showed fast drug release. Thus the *in-vivo* release of gabapentin did not correlate with the *in-vitro* release of the drug.

Conclusion:

It can that the floating use as a proportional alternative of conventional dosage forms. The *in-vivo* release of the gabapentin does not correlate with the *in-vitro* release of the drug. Increasing the concentration of the drug in the tablet was not followed by an increase in the AUC and C_{max}.

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