
بسم الله الرحمن الرحيم

Thermally Reversible In Situ –Gelling Carbamazepine Liquid suppositories

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Introduction

- Carbamazepine is indicated for the control of epilepsy ,Trigeminal neuralgia ,and acute mania.
- It undergoes extensive hepatic first- pass elimination after oral administration.
- The rectal administration of CBZ has been reported in human ,using suspensions or suppositories.
- A rectal dosage form of CBZ is not commercially available , although it is of particular interest when oral administration is impossible .

Objective

To examine the potential use of in situ gel formulation for rectal administration of CBZ .

Preparation of Liquid Suppsitories

Formulations	composition
Poloxamer 407(P407)	20%P407+1%sod.deoxycholate
P407 +carbopol	20%P407+0.5%carbopol+1%sodiumdeoxycholate
P407+MC+carbopol	20%P407+!%MC+0.5%carbopol+ 1%sodium deoxycholate
P407+P188+carbopol	20% P407+15%P188+0.5%carbopol +1%sodium deoxycholate
Gelrite	0.3% Gelrite +1%sod. deoxycholate

Measurement of Gelation Temperature

Gelation temperature was measured using the method reported by Choi et al.,1998 & Miyazaki et al.,1991.

Measurement of Gel Strength

Gel strength of the formulated liquid suppositories was determined using the method reported by choi et al.,1998.

Measurement of In Vitro Bioadhesion

In vitro bioadhesion of the prepared gel formulations was examined using the isolated rabbit's ractum.

Measurement of Rheological Properties

Brookfield Viscometer

Drug Release From Liquid Suppositories

Apparatus: USP paddle method.

Medium: 900 ml of phosphate buffer at pH 7.4 containing 0.2%Tween80.

Stirring rate: 50 rpm.

Sampling: one ml aliquots were collected up to 2 h.

Assay: spectrophotometrically at 284 nm.

In Vivo Study

- For each examined formulation, six New Zeland rabbits are used .
- Liquid suppositories were administered at a dose of 200 mg CBZ into the rectum 3 cm above the anus .
- For oral administration, 2 ml suspension containing 200 mg CBZ (particle size <125 um) was administered.
- Blood samples were collected from the ear vein.
- Assay: HPLC assay at 220 nm.

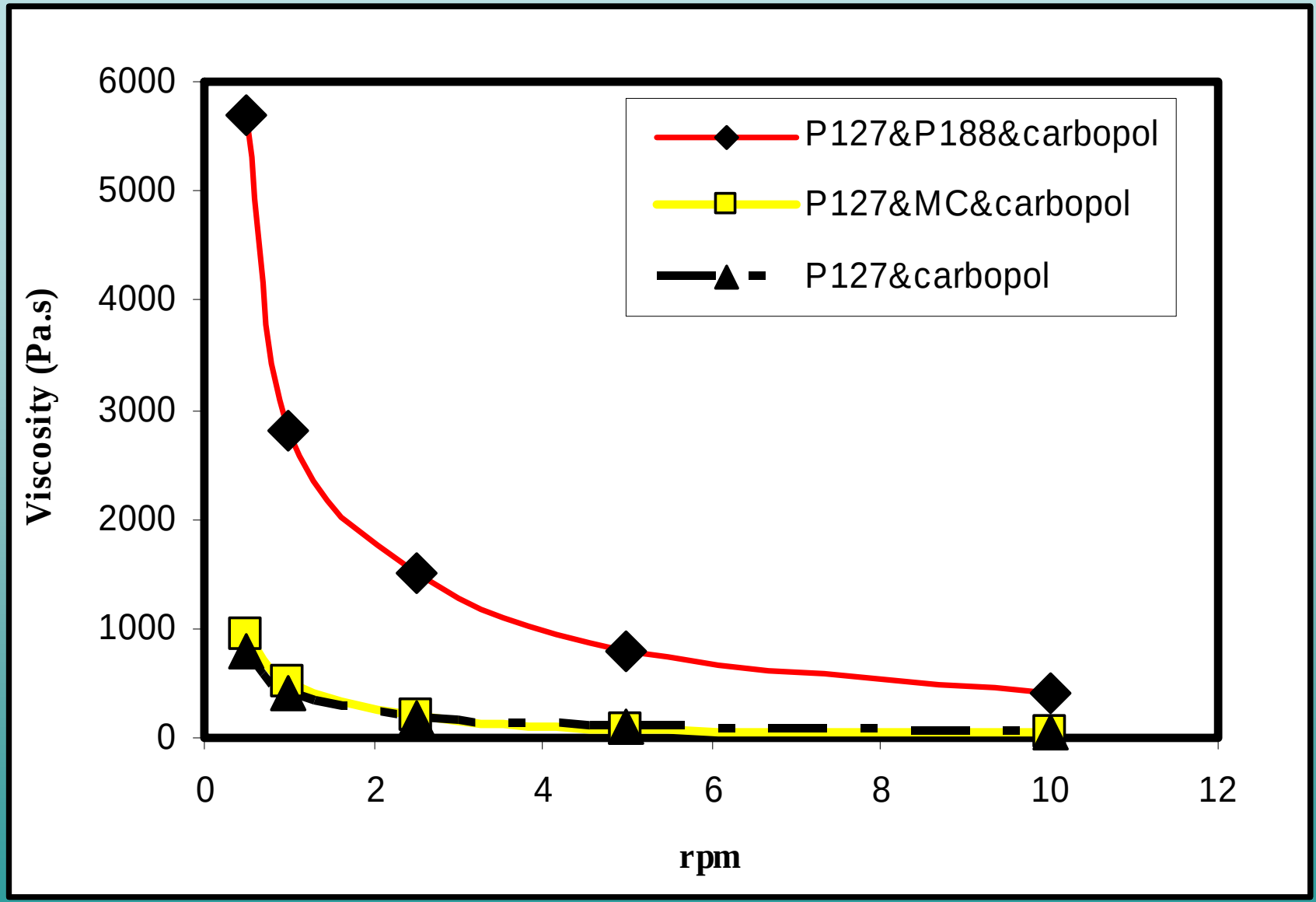
Pharmacokinetic Analysis

C_{max} (μg), T_{max} (h) , AUC_{0-7h}, and $AUC_{0-\alpha}$,(μg.h/ml) and the relative bioavailability(F_{rel}) were calculated.

$F_{rel} = \{AUC_{0-7h}$ (tested formula)/ AUC_{0-7h} (susp.)$\}$ x100 .

Results and Discussion

Formula	Gelation Temp.± SD (°C)	Gel Strength (g)	Bioadhesive Force (dyne/cm)
P407-P188 Carbopol	30 + 0.4	650+ 15	8820+20
P407-MC carbopol	30+0.3	530+10	16170+50
P407-carbopol	23+0.5	550+8	7350+20

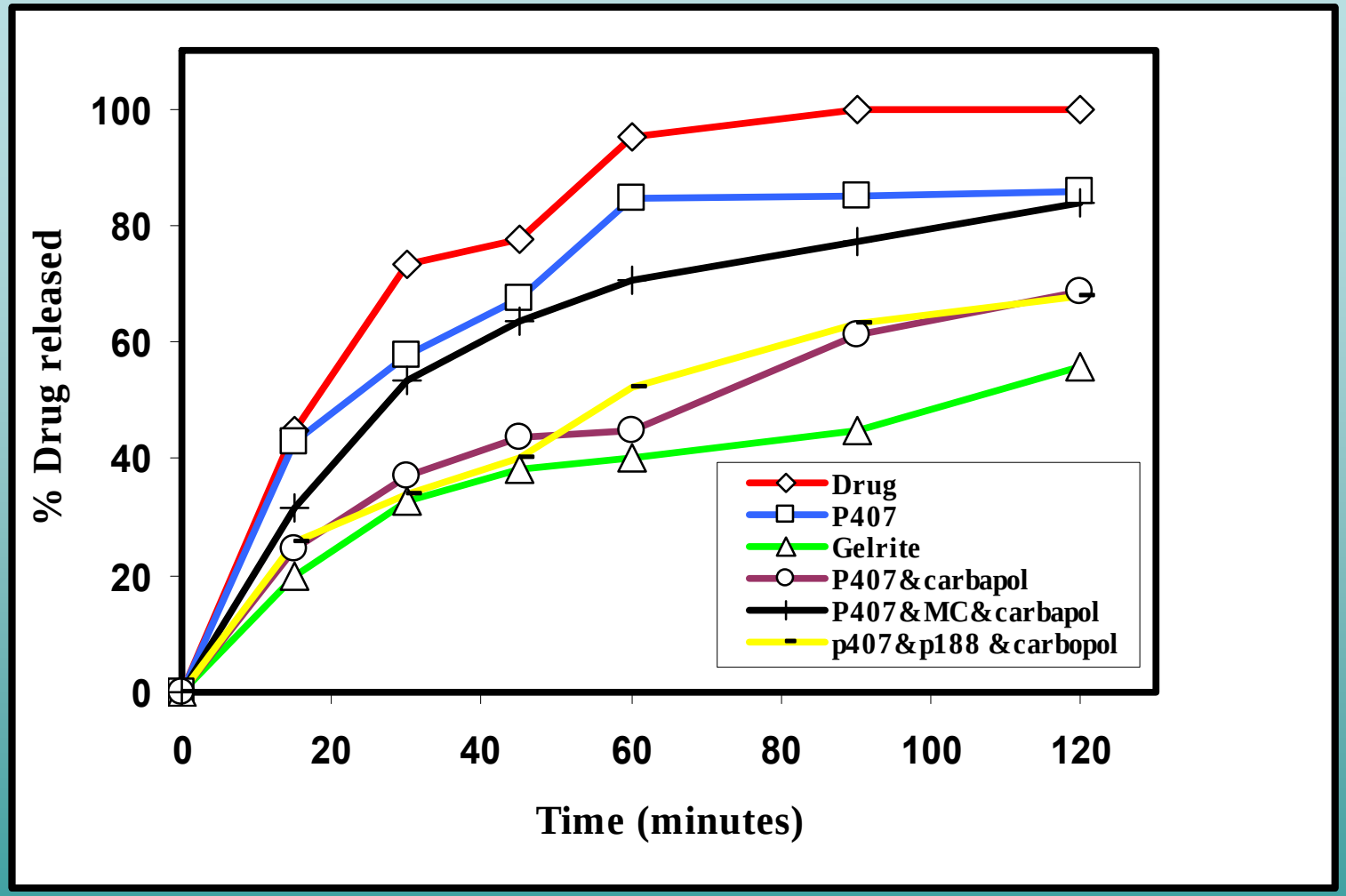


Rheogram of Various Prepared Formulation

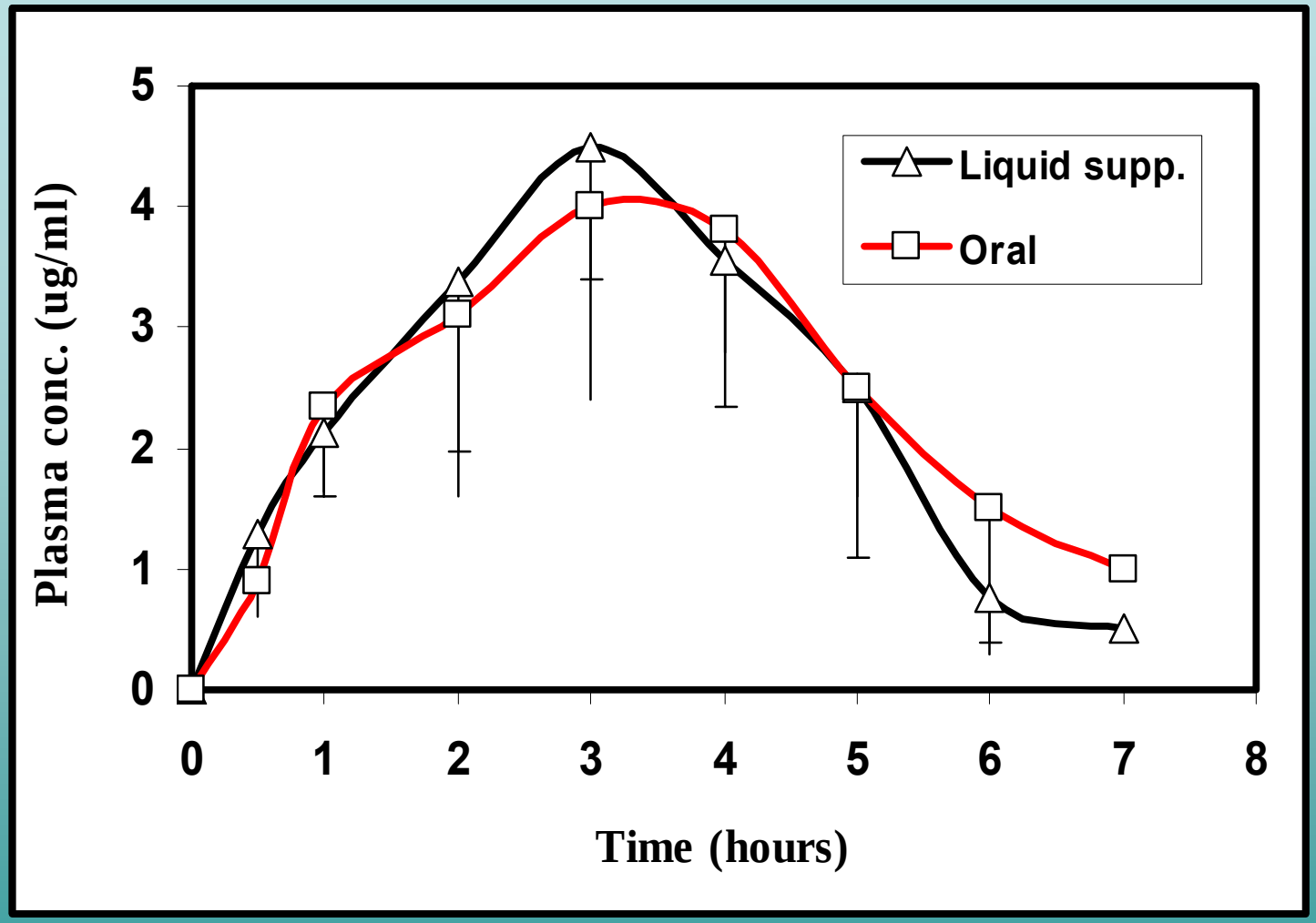
Release Kinetic Parameters Calculated From Peppas Equation*

Formulations	K	n
Drug	0.293	0.299
P407	0.173	0.354
Gelrite	0.064	0.451
P407-carbopol	0.067	0.484
P407-P188-carbopol	0.066	0.493
P407-MC-carbopol	0.104	0.454

*$M_t/M_\alpha = Kt^n$



Release of Carbamazepine From Various Liquid Suppository Formulations



Plasma Concentration-Time Profile of Carbamazepine Liquid Suppository and Oral Suspension

Pharmacokinetic Parameters of Carbamazepine Liquid Suppositories and Oral Suspension

Prameter	P407-MC-Carbopol Liquid Suppositories	Oral CBZ Suspension
$AUC_{0\text{-}7h}$(μg.h/ml)	17.2	17.6
$AUC_{0\text{-}\alpha}$ (μg.h/ml.)	17.9	18.8
T_{max} (h)	3.0	3.0
C_{max}(μg/ml)	4.5	4.0
F_{rel}%	97.7	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