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Synthesis and Evaluation of Some New Psychotic Polymeric Drugs.

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ABSTRACT

Microparticles polymer contain anti-psychotic drugs were prepared for oral delivery system. Choropromazine hydrochloride, Carbamazepine and Valproic acid were used in this study. Chitin and gelatin cross linked with glutaraldehyde was prepared as microparticals. Also both chitin and tetramethylol urea were used to prepared polymer prodrug of Valproic acid. All the polymeric drug were subjected to various physicochemical studies, such as Fourier Transform Infra-Red spectroscopy (FT-IR). Physical state of drug in the microparticles was determinate by Differential Scanning Calorimetry (DSC). In vitro drug release indicated, the possibility to design a controlled drug delivery system for the prolonged release of drugs. Generally 50% of the drugs were released after 30 min, therefore its improving therapy by possible reduction of the time intervals between administrations.

Keywords: anti-psychotic drugs, microparticles, polymeric prodrugs.

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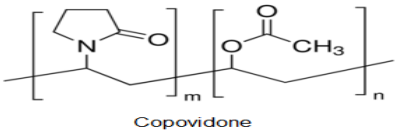
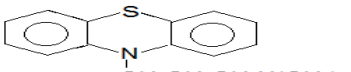
INTRODUCTION

Use of novel drug delivery methods could enhance the efficacy and reduce the toxicity of antiepileptic drugs (AEDs)[1]. Slow-release oral forms of medication or depot drugs such as skin patches might improve compliance and therefore seizure control. In emergency situations, administration via rectal, nasal or buccal mucosa can deliver the drug more quickly than can oral administration. Slow-release oral forms and rectal forms of AEDs are already approved for use, nasal and buccal administration is currently off-label and skin patches for AEDs are an attractive but currently hypothetical option. Therapies under development may result in the delivery of AEDs directly to the regions of the brain involved in seizures. Experimental protocols are underway to allow continuous infusion of potent excitatory amino acid antagonists into the CSF. In experiments with animal models of epilepsy, AEDs have been delivered successfully to seizure foci in the brain by programmed infusion pumps, acting in response to computerized EEG seizure detection [2].

Vinylpyrrolidone/vinyl acetate copolymer (VP/VAc) (Copovidone) was used for the enhancement of dissolution rate of tegretol, an antiepileptic drug characterized by very low water solubility [3].



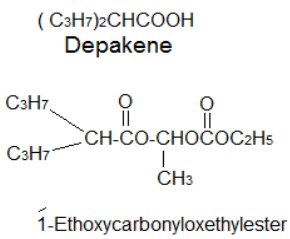
Copovidone



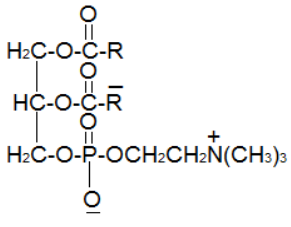
Tegretol

In particular, nanocapsules of polyethyl cyano acrylate (PECA) were prepared. The possible mechanism of formation and the influence of preparation conditions on the quality of nanocapsule formulations were investigated by freeze-fracture electron microscopy and laser light scattering using both the inverse Laplace transform and the standard cumulant analysis for data fitting. High-quality nanocapsule systems were obtained using an aprotic fully water-miscible organic solvent such as acetone. Three antiepileptic drugs (Ethosuximide, 5,5-diphenyl hydantoin and tegretol) were entrapped in PECA nanocapsules. By encapsulating the three antiepileptic drugs in the PECA nanocapsules, it was possible to achieve controlled drug release [4].

Another type to improve AEDs is Prodrugs are comprised of a drug attached to a distinct compound that is removable via enzymatic cleavage or hydrolysis *in vivo.* The prodrug is inactive; an active drug is formed by liberation from the prodrug, with the release of an additional compound or moiety. The attached moiety can serve to make the prodrug more lipophilic, therefore increasing its tendency to cross the BBB[5]. A prodrug of valproic acid DP-VPA ,was developed by this strategy,DP-VPA is synthesized by linking depakine with lecithin , a phospholipid which ensures the inactivation of the parent drug in the systemic circulation [6]. the recently, prepare a novel and useful 1-ethoxycarbonyloxyethylester with less ulcerogenicity when administered orally than with valproic acid from which it is derived. The novel ester acts as a prodrug exhibiting characteristics of a slow release profile of the parent drug, from, which it is derived, and it is suitable for the satisfactory control of the epileptic patient , it is sufficient to administer it twice or even once a day[7].



1-Ethoxycarbonyloxethylester



Lecithin

Valproic acid and its ester derivatives are relatively new drugs that are now in common use, are reported to biotranform to valproic acid before reaching the systemic circulation and therefore can be considered to be a valproic acid pro-drug[8].

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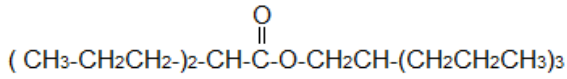
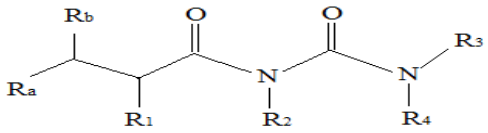


2-propylpentanol-di-n-propylacetate

Chitin is the most abundant natural amino polysaccharide and is estimated to be produced annually almost as much as cellulose. It has become of great interest not only as an underutilized resource, but also as a new functional material of high potential in various fields, and recent progress in chitin chemistry is quite noteworthy. The purpose of this review is to take a closer look at chitin and chitosan applications [9].

The binding force that holds the drug to the microparticles can be physical or chemical. In addition to this, hydrophobic and electrostatic interaction may also exist. Depending on the force of attachment. The drug release is expected to be faster if only physical entrapment is achieved. Drug release in such cases is modulated by a diffusion controlled mechanism. Slow release can be achieved by chemically binding the drug to the microparticles. The polymer microparticles should have reactive functionalities to which the drug can be bound through a functionality available on the drug[10]. Drugs can be attached onto a polymer-drug conjugate prepared by attaching the drug to the polymer chain can be further into the microparticles. The linkage should be susceptible to degradation in the physiological environment so that the drug is released from the microparticles. High loading is possible if sufficient functionalities to which drug can be bound exist on the polymer microparticles. The drug release in this case will depend on the rate of cleavage of the bond linking the drug to the microparticles[11].

Novel acyl urea containing compounds uses in the treatment neurological diseases and disorders such as epilepsy, neuropathic pain bipolar disorder:status epileptics, chemically-induced convulsion and/ or seizure disorders[12] .



R_1 , R_4 , H or Alkyl
R_1 = alkyl C 3-10 , R_a --R_b =CH_3
R_2= R_4 = H

The goals of this research are prepare of some new microparticles contain anti-epileptic drugs (Choropromazine and Carbamazepine) for prolong release of drugs. Also polymeric prodrugs of Valproic acid is prepare.

MATERIALS AND METHODS

Materials

All chemicals and solvents used were of analytical grade (Analar or BDH) and were used without further purification.

Methods

Preparation of microparticle [13]

Without drug

Chitin and gelatin were dissolved in dilute acetic acid solution (5% HAC) together at concentration of 1:1 by weight. A certain amount of tween-80 and liquid paraffin at water to oil ratio of 1:10, were added drop wise to Chitin/gelatin mixture under agitation at 650 rev./min. at 30 °C. A suitable amount of 25% aq.

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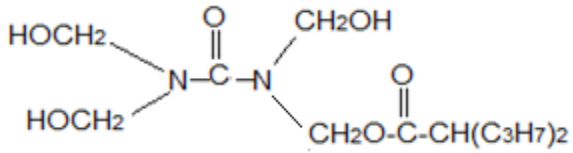
Glutaraldehyde solution was added for 2 hours ,finally the result washed three times with water, then with petroleum ether (60°C- 80°C) to remove the adhered liquid paraffin and to obtain microparticle.

With loading drugs Choropromazine and as microparticales (A) and (B) respectively

Dissolving chitin/gelatin (1:1) by weight and drugs Choropromazine and Carbamazepine, 100 mg (0.28 mmol), 200 mg(0.84mmol) respectively was dissolved in the above polymeric solution. Microparticles were prepared by exactly the same method as mention above.
The products were characterized by FT-IR and DSC.

Preparation of Tetramethylol urea(TMU)- Valproic acid (C) [14]

250 three neck round bottom flask, contain mechanical stirrer and condenser ,was charge with 6 gm (0.1 mole) of urea dissolved in 45 ml (1.63 mol) of formalin (37 % w/v) and 10 gm (0.25 mol) NaOH . The reaction mixture was heating to 60 ˚C with good stirring for 3 hours in water bath. The mixture was cold and the pH was adjusted to 9-11. The solvent was evaporated by rotary evaporator .the product was dissolved in methanol and filter off .the solvent was evaporated. The oily product was collected. Then react tetramethylol urea with valproic acid (1:1 mole) with two drop from conc. Sulphuric acid to produced TMU-valproic acid.



TMU-Depakene

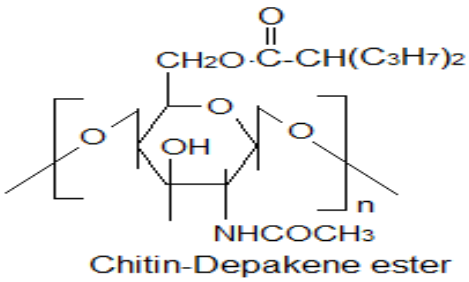
Preparation of Chitin-Valproic acid ester as polymeric prodrug (D) [15]

preparation Valproic acid acyl chloride:

Fit a 100 ml two-necked flask with a dropping funnel and a reflux condenser. Place 3.6 gm (0.025 mol) of valproic acid in the flask, heat on a water bath and added 8.92 gm (0.074 mol) of thionyl chloride during 45 minutes, shake the flask from time to time to ensure mixing , reflux for 30 minutes and isolate the acyl chloride by distillation.

Preparation of polymeric prodrug Chitin - Valproic acid:

4 gm (0.025 mol) of valproic acid acyl chloride was added slowly to chitin solution 0.236 gm (0.0011 mol) dissolved in less amount of 5 % (acetic acid)with stirrer ,left the reaction overnight with close the round flask of the reaction, the solvent was evaporated and resulted soild products was collected and dried under vacuum to give chitin-valproic acid ester, that re-crystallized by using absolute ethanol.



Chitin-Depakene ester

***In vitro* release study [16]**

In vitro evaluation of microparticles loading drug was done using standard method 20 mg of each microparticles were dispersed in 400 ml of phosphate buffer 0.1M (pH 6.6) in a conical flask and maintained at

37± 0.2 ˚C under continuous shaking. At selected time intervals, 5 ml samples were withdrawn through a hypodermic syringe fitted with a 0.4 Mm Millipore filter and replaced with the same volume of prewarmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrometrically at selected wavelength, Choropromazine and Carbamazepine at λ_{max}(2254 and 287nm) respectively .The release drug content was computed from the calibration curve.

Infra-Red Studies [11]

Chemical interaction between the drug and the polymeric material was studied by using Fourier transform infrared spectroscopy (FT-IR). Infrared (FT-IR) spectrum of the drug ,drug loaded polymers, blank polymers and physical mixture of drug and empty polymers were recorded using FTIR(Shimadzu Bruker model Equinox 55) spectrophotometer using KBr disc (400-4000 cm^{-1}).

Defferential Scanninc Colorimetry (DSC) Studies

The physical state of some microparticles loading drug was analyzed by DSC (Mettler-Toledo Sta 822 system, Switzerland). The thermograms of the sample was obtained at a scanning rate of 10 ˚C/min. conducted over a temperature range 25-220˚C respectively.

RESULTS and DISCUSSIONS

Fourier transform infrared was used to studies the interaction between drug and in the both microparticles and polymeric prodrug. Infrared spectrum of blank polymers, polymeric drugs and physical mixture of polymer loading drugs were recorded to estimate the distinguish bands as shown in table (1). The stretching vibration of hydroxyl group of tetramethylol urea at 3040-3680 cm^{-1}. The sharp peak of hydroxyl group was broaded in the tetramethylolurea-valproic acid prodrug (3150-3700cm^{-1}) due to formation hydrogen bond between hydroxyl group of methylol group or with carbonyl group C=O ester which appearance at 1710.7 cm^{-1} .

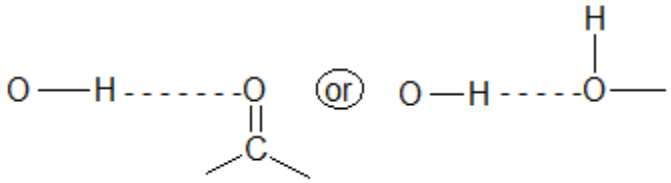


Table 1: Shows the important FT-IR Spectrum bands of compounds.

Compounds	Streaching vibration bands(cm^{-1})				Bending band vibration (cm^{-1})	
	OH	CH_3,CH_2	C=O	C=C	OH	C-O-C
A	3400 w	2950	1600	1550	1400	1050
B	3450	3000	1604	1500	1440 w.	1110
C	3382.9	2935,2874	1710.7	-----	------	1000
D	3340	2960,2875	1740	-----	-------	1250

The polymer prodrug of chitin-valproic acid (C), appearance of new strong band, at 1740 cm^{-1} can be attributed to the stretching vibration of ester (-CO.O-) group. The microparticles of both Choropromazine and carbamazepine on chitin-gelatin cross linking were prepare. The microparticales were physical interaction between drug and polymers. FT-IR spectra of all microparticales were not shown new covalent bonds. The infrared spectrum was shows hydrogen bond in the broad band of hydroxyl group at 3500 cm^{-1} position, also red shift in the most bands. both the stretching vibration and bending of all products in infrared spectrum was shown in table 1.

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Differential scanning calorimetric (DSC) thermo gram data was shown in table 2. Generally all the thermo gram was increased in microparticales of polymer loaded drug compare with free polymer. Both the change of enthalpy (ΔH_m) and the change of entropy (ΔS_m) in the melting point were reduced in T_m when the drugs incorporate in polymer matrix.

Table 2: DSC thermogram data of microparticales and polymeric prodrug.

Compounds	t_i	$t_{op.}$	$t_{fin.}$	ΔH_m Kj/mol	ΔS_m J/ mol.k	T_m (˚C)
Microparticle	37.5	111.3	187.5	4.915	6.4104	220.75
	199	220.75	265.5			
A	56.4	123.38	181	12.17574	21.4744737	293.98
	254	293.98	339			
B	75	133	187	44.32	109.16	109.16
D	50	128.07	190	5.0147	9.97999	229.48
	210	229.48	240			

ΔH_m = enthalpy of melting , **ΔT_m** = temperature of melting
ΔS_m = the change of entropy in the melting point, **t_{op}** = **T_m**

In order to confirm the physical state of the drug in the microparticales, DSC of the drug-crosslinkage polymer , drug loaded polymer (microparticales) were shown in figures (1- 4). Generally the physical mixture of drug and polymer (microparticales) showed the same thermal behavior as the individual component indicating that there was no or week interaction between the drug and the polymer in the solid state.

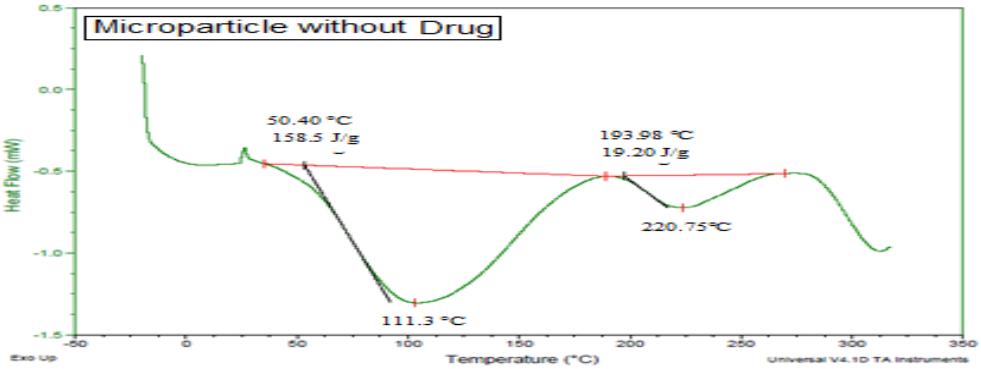

Figure 1: DSC thermogram of microparticle.

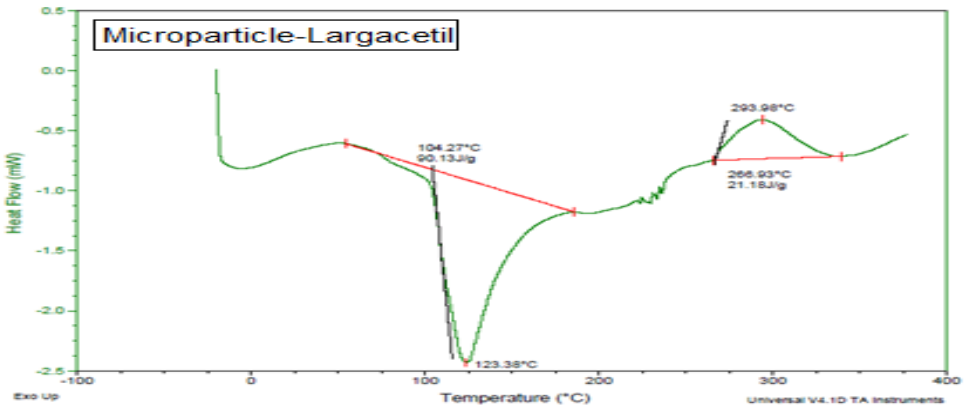

Figure 2: DSC thermogram of compound A.

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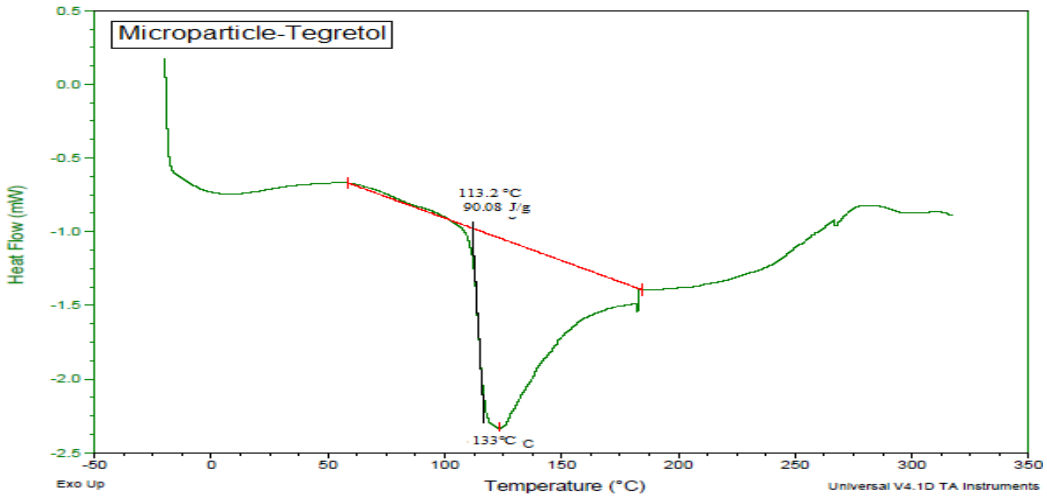

Figure 3: DSC thermogram of compound B

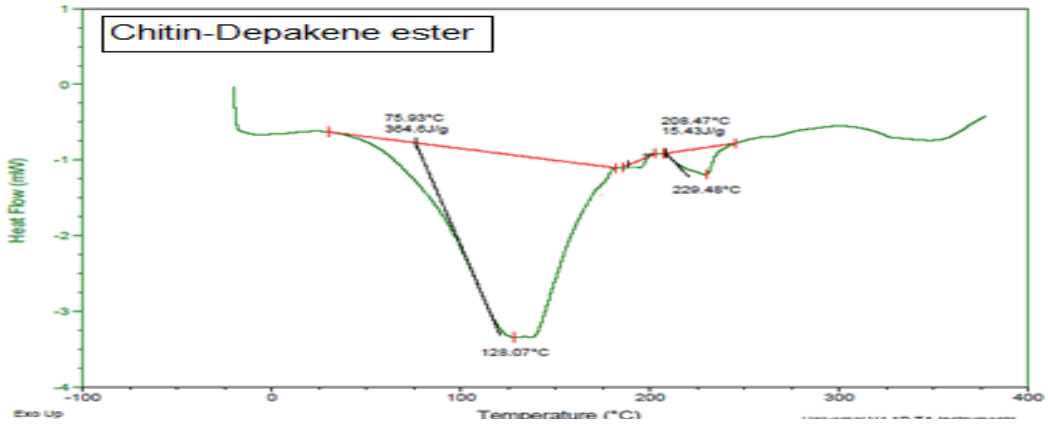

Figure 4: DSC thermogram of compound D .

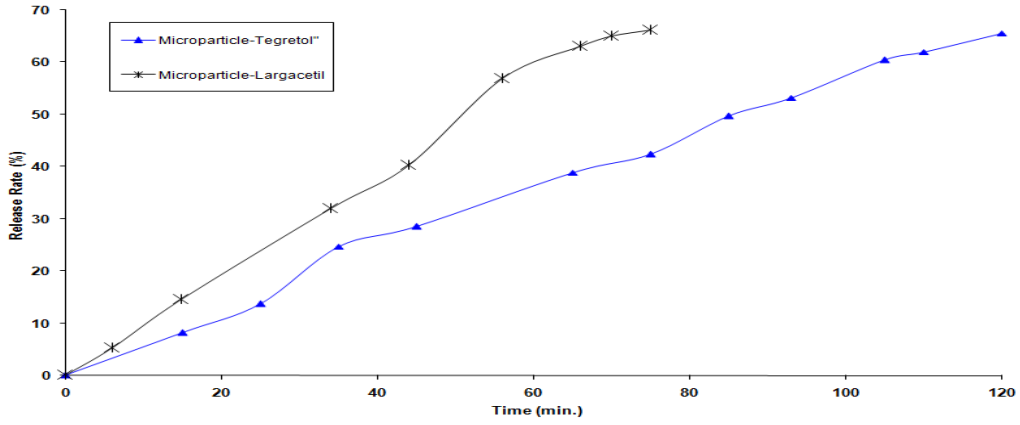

Figure 5: The release of drug from microparticles A and B

The DSC thermo grams data showed that the drugs were incorporated within the polymer structure as indicated by disappearance of endothermic melting peak of the active gradient or the melting takes place at lower temperature due to the linkage of the drug to polymer structure [17]. The absence of endothermic peak of the drug in the DSC of the drug loaded polymers, suggests that the drug existed in an amorphous or disordered crystalline phase as a molecular dispersion in polymeric matrix [18,19].

The in vitro release of carbamazepine and valproic acid microparticles were carried out in pH 6.8 . The microparticles were swelled in the solution environment but not dissolved. Generally 40-50% of the drugs

were released after 30 min., it was concluded that the 20% release also may be due to the presence of unincorporated drug on the outer surface of the microparticales. It was observed that the rate of release decreased as the concentration of the carrier was increase .this may be due to low permeability of polymer to the drug[11]. A sustained release microparticales preparation which is produced by including antiepliptic drug such as Choropromazine, carbamazepine and valproic acid or like into a base composed of a high molecular weight polymer having in vivo histocompatibility such as chitin co gelatin or the like the hydrophobic antipsychotic drug such as Choropromazine was applied. The base that constitutes the sustained release microspheres of the present invention should have such a function that its concentration in blood plasma can be maintained at a constant level by a single administration whereby its time.

The ester linkage of polymeric valproic acid with both tetramethylol urea and chitin was shown not release at seem conditions, but its show little release after 24 hrs (12%) due to covalent bond. A biodegradable high molecular weight polymer(s) (2000-80,000) is decided by the drug-releasing rate, period and the like, and may be controlled within the range of from about 0.2 to about 10,000 times by weight of the drug, it is preferred that the polymer is used as the base of microparticles preparation of the present invention in amount of from 1 to 1000 times by weight of the drug [20].

Controlled drug delivery technology represents one of the frontier area of science, which involves multidisciplinary scientific approach, contributing to human health care, these delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity and improved patient compliance and convenience [20].

CONCLUSION

Chitin-Gelatin micropaeticles exhibited a significant bioadhesive property and could potentially be used as a bioadhesive microparticles for controlled and sustained release of some CNS drugs, anti-depressant drugs. Polymeric prodrug were shawn prolong sustained release compare with microparticales.

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