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Formulation of chlorpromazine Bio-nano gel using a bio-retardant from *Prunus amygdalus* for nose to brain targeting.

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Abstract

Nanoparticles (NPs) could be an exciting prospect for transnasal drug delivery as they have higher surface area to cover highly vascularised nasal absorptive area providing a greater concentration gradient. NPs are used as a sustained drug delivery system. NPs , interacts with mucus to prolong the residence time of drug carrier at the drug absorption sites and protected the entrapped drug from enzymatic degradation until they are absorbed. Therefore, the bioavailability of drug is improved. Our research work aimed to formulate bio-nano particles loaded with chlorpromazine using a novel bio-retardant from *Prunus amygdalus.* The bio-polymer was isolated by novel method by addition of non aqueous solvent. Five formulations were prepared using Chlorpromazine, and *Prunus amygdalus* as bio-polymer, and five from the synthetic polymer Pullulan gum varying concentration of bio-polymer and synthetic polymer. The nano-particles were prepared by solvent evaporation method and were evaluated for drug content entrapment efficacy in-vitro drug release in-vivo studies and stability studies. On the basis of in-vitro drug release in-vivo, pharmacokinetic data and muco adhesivity FA8(1:15) displayed the best results whose R^2 value was 0.9179 and Fickian Diffusion as mechanism of release hence selected as the best formulation depicted by bits software. Delivery of API molecule to the brain for the management of depressive disorder is significant, minimizes the ADR and side effects of therapeutic molecule and offer good patient compliance through this novelistic approach.

Keywords:

1. Introduction

An ideal drug therapy achieves effective concentration of drug at the target for a specified period of time in order to minimize general and local side effects. The targeting of drug to brain is the difficult task. The reason for these difficulties may range from physiological build up to limited pharmaceutical advancement in concerned topic. To overcome this barrier and enhance potential therapeutic agents accessing to the brain, sophisticated approaches such as Nose to brain drug delivery systems can be employed. Nose to brain drug delivery can be adopted as a reliable, easy and advanced drug delivery route.

Many recent literatures present those using nanoparticles delivery systems after intravenous injection could successfully deliver drugs into the brain by several mechanisms. Nanoparticle delivery system combines the advantages of a prolonged activity in target tissue, an increased longevity and stability of the carrier and carrier incorporated drug, and reduction of drug-associated side effects. So, delivering drug by administering nanoparticle via nose to brain can be regarded as a novel approach.

1.1 Anatomy of brain:

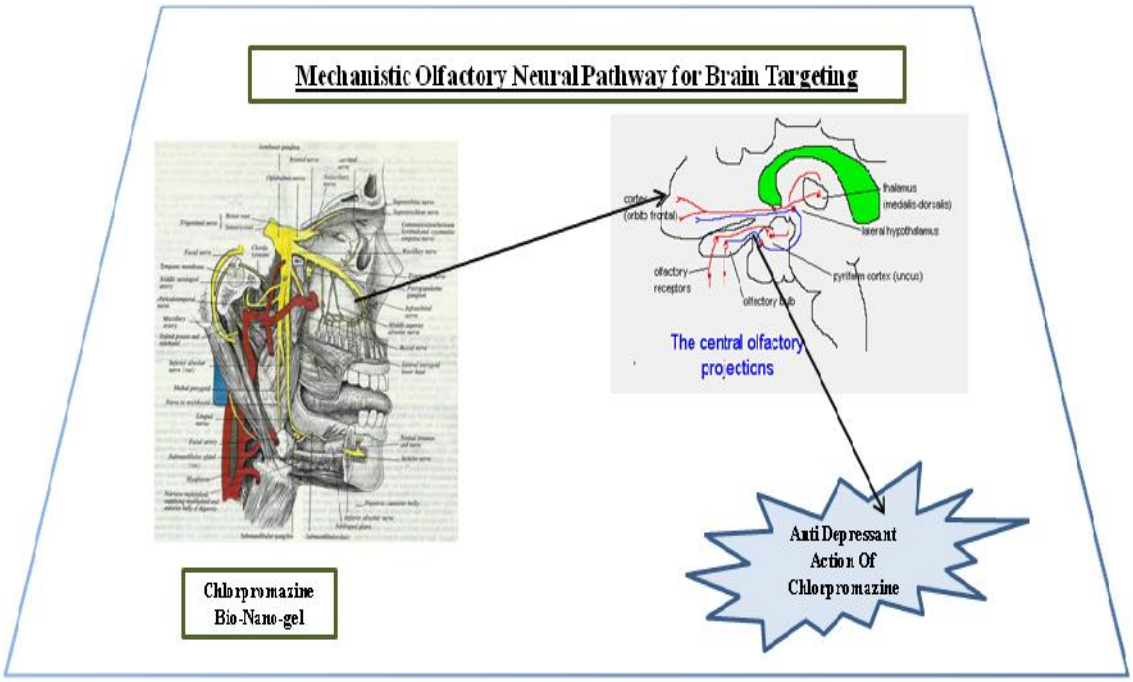
The brain is probably one of the least accessible organs for the delivery of drugs due to the presence of the blood–brain barrier (BBB) that controls the transport of endogenous and exogenous compounds, thus providing the neuroprotective function. The structural BBB is formed by the cerebral capillary endothelial cells that, in contrast to endothelial cells in capillary blood vessels in most other tissues, are closely joined to each other by tight junctions produced by the interaction of several transmembrane proteins. Essential compounds such as amino acids, hexoses, neuropeptides, and proteins employ these transporters or specific carriers to permeate the brain [1,2]

Lipophilic solutes are able to diffuse across the BBB by direct permeation through the cell membrane if their molecular weight is not more than 500Da. [3]

Mechanisms [4]:

The most obvious possibility is that there direct transport to the brain along the olfactory nerve. There are numerous other potential routes to the brain following intranasal administration. One such mechanism arises because the olfactory receptor neurons regenerate every 3-4 weeks (due to their regular contact with toxins in the environment) and as a result nasal barriers to the central nervous system are rather porous. The special cells that ensheath the olfactory receptor neurons don't decay but remain intact to guide the regrowth of the olfactory receptor neurons. Thus they could provide another direct route to the brain via fluid filled extracellular channels during neuron regeneration. In other words these channels could allow for extracellular transport of drugs in addition to travelling along the axon of neuron themselves

Figure 1



Pathways:

The olfactory epithelium is a gateway for substances entering the CNS and the peripheral circulation. The neural connections between the nasal mucosa and the brain provide a unique pathway for the non-invasive delivery of therapeutic agents to the CNS [5-7]. The olfactory neural pathway provides both an intraneuronal and extraneuronal pathway into the brain. The intraneuronal pathway involves axonal transport and requires hours to days for drugs to reach different brain regions. While the extraneuronal pathway probably relies on bulk flow transport through perineural channels, which deliver drugs directly to the brain parenchymal tissue and/or CSF. The extraneuronal pathway allows therapeutic agents to reach the CNS within minutes [8-11].

Intranasal delivery of agents to the CSF is not surprising as CSF normally drains along the olfactory axon bundles as they traverse the cribriform plate of the skull and approach the olfactory sub mucosa in the roof of the nasal cavity, where the CSF is then diverted into the nasal lymphatic [12-14]. The transport of drugs across the nasal membrane and into the bloodstream may involve either passive diffusion of drug molecules through the pores in the nasal mucosa or some form of non-passive transport [15].

2. Materials and Methods

2.1 Isolation of bio-material from the seeds of *Prunus amygdalus*

250 grams of Prunus amygdalus kernels were soaked in distilled water for 24Hrs. The outer cover was removed, and was grinded into a paste. 300 ml water was added to the paste and it was filtered through a muslin cloth. The filtrate was centrifuged at 3000 rpm to remove the residual matter. The optimization was performed by taking 2ml of the filtrate and 2ml of various non aqueous solvents the maximum yield was obtained with prop none, hence used as the solvent for extraction. The remaining filtrate was added with equal quantity of prop none and kept in refrigerator for 24hrs. The settled bio-material was separated by centrifugation at 4000rpm for 10 mins.The bio-materials was dried in vacuum desiccators for 48 hrs The process of bio-material extraction was repeated 6 times & practical yield was calculated. The % yield for *P. amygdalus* was found to be 10.2±2.33% with a color changing point of 275˚C±5˚C. The bio-materials were purified and no presence of chlorides, sulphates and starch was observed

2.2 Physico-chemical characterization of the bio-polymer:

The isolated bio-material was white in color, odorless, characteristic taste, partially soluble in water, color changing point of 270-275˚C. It had a viscosity of 1.54 cps, carbohydrates were absent while proteins were present.

Table1: Characterization

1.	Color	White
2.	Odor	Odorless
3.	Taste	Characteristic
4.	Solubility	Partially soluble in water
5.	Melting point	270-275
6.	Proteins	Present
7.	Carbohydrates	Absent

The **IR spectra** revealed the presence of tertiary(1078.13 cm^{-1}), secondary alcohols,(1151.13 cm^{-1}) aromatic rings(1598.88 cm^{-1}) and the presence of alkanes, alkenes(2925.81 cm^{-1}) and nitro compounds along with ketones(1678.5 cm^{-1})**(fig. no2).** These groups like the ketonic groups, nitro groups indicate the mucoadhesive activity of the bio-polymer as these groups are observed in the mucoadhesive polymers like HPMC, polycarbophil. The SEM analysis pf the bio-polymer revealed that it has a smooth surface with no rough edges. It shows the smooth, amorphous nature of the bio-polymer.the bio-polymer showed a morphological structure similar to the polymers and hence it confirms the polymeric nature of the bio-polymer (**Fig 3**).

2.3 screening of the isolated bio-polymers for mucoretentivity:

The isolated bio-polymers were screened for mucoadhesivity. The results revealed excellent mucoretention ability and filmability. The bio-polymeric solutions had very good mucoadhesivity in a concentration ranging 2%-6%.

2.4 Drug interaction study:

The drug interaction study revealed that there was no interaction between the drug and the excipients including the bio-polymers. This was proved by the result of the thin layer chromatography in which no change was seen in the RF value in the TLC method.

Also there was no change in the ƛ max. Value which was observed to be 258 nm prior to the test and after the test it was 258 nm hence confirming that there was no interaction between the drug and excipients.

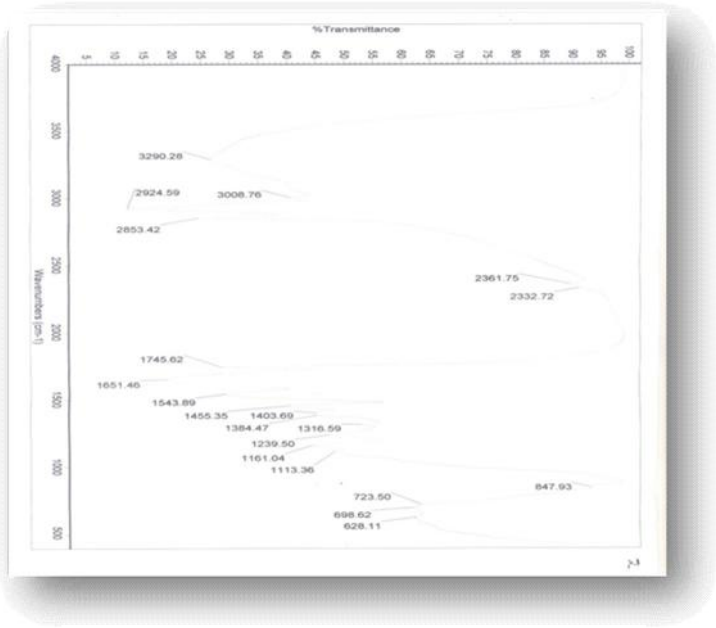


Fig 2. IR Spectra of *Prunus amygdalus*

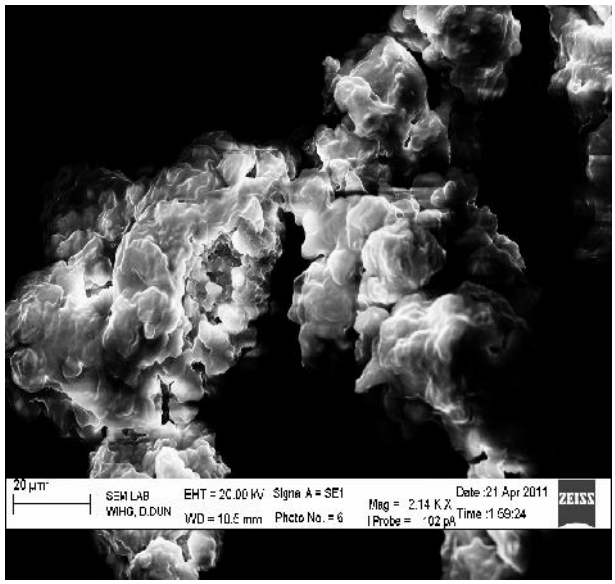


Fig 3. SEM of *Prunus amygdalus*

No observable signs of drug interaction were seen. It was conclude that none of the excipients had a detrimental effect on the drug and could be safely used for the formulation of the bio-films.

2.5 Acute toxicity studies:

The results of the acute toxicity studies revealed safety profile. They did not show any signs of toxicity, change in body weight, changes in the skin, corneal reflex, respiratory rate, autonomic symptoms, salivation, diarrhea, lethargy, sleep, behavioural patterns, and convulsions. The test group was comparable to the control group of animals. Hence it was concluding that the isolated bio-polymer was safe and non-toxic.

2.6 Formulation of CPZ bio-nanoparticles loaded with *Prunus amygdalus* biopolymer

Table 2: Formulation Table

Formulations	FA2 (1:0.5)	FA4 (1:5)	FA3 (1:10)	FA8 (1:15)	FA7 (1:20)
Drug: polymer ratio	1:0.5	1:5	1:10	1:15	1:20
chlorpromazine(mg)	10	10	10	10	10
Prunus amygdalus Bio-polymer (mg)	0.5	5	10	15	20
Glycerin µl	60	60	60	60	60
Distilled water(ml)	5	5	5	5	5
Buffer (ml) pH 5.5	5	5	5	5	5

2.7. Formulation of CPZ bio-nanoparticles loaded with phullulan gum *(pg)*:

Chlorpromazine bio-nanoparticles using standard polymers phullulan gum were prepared by using "Novel method ".In this method the standard polymer was accurately weighed in different ratios and treated with glycerine (0.24gm), glycerine is used as a wetting agent, and then to this slurry distilled water (5ml) was transferred into mechanical stirrer. The drug (10mg) solution was prepared separately with methanol (5ml). The drug solution was added to the polymeric solution under stirring 4,500 RPM until the formation of nanoparticles for about half an hr. The beaker containing the sample was subjected for 5 cycles of sonication for 3min. The sample was micro-centrifuged at 5000 RPM for 10mins, and was dried at room temperature for 24hrs.

Table 3: Formulation Table:

Formulations	Fpg2 (1:0.5)	Fpg4 (1:5)	Fpg9 (1:10)	Fpg7 (1:15)	Fpg6 (1:20)
Drug: polymer ratio	1:0.5	1:5	1:10	1:15	1:20
chlorpromazine(mg)	10	10	10	10	10
Pullulan gum(mg)	0.5	5	10	15	20
Glycerin (µl)	60	60	60	60	60
Distilled water(ml)	5	5	5	5	5
Buffer (ml)pH 5.5	5	5	5	5	5

3. Results

The content uniformity of FA1-FA5 was found to be 92.7±0.1% - 97.4±0.05%.having pH 7-8 out of ten formulations five were prepared by the almond bio-polymer and five from the synthetic biopolymer FA8 (1:15) was found to be best formulation was whose R^2 value was 0.9179 and best fit model higuchi matrix, Fickian Diffusion as mechanism of release having t_{50} of 338.16 hrs. The release kinetics was depicted by BITS software.

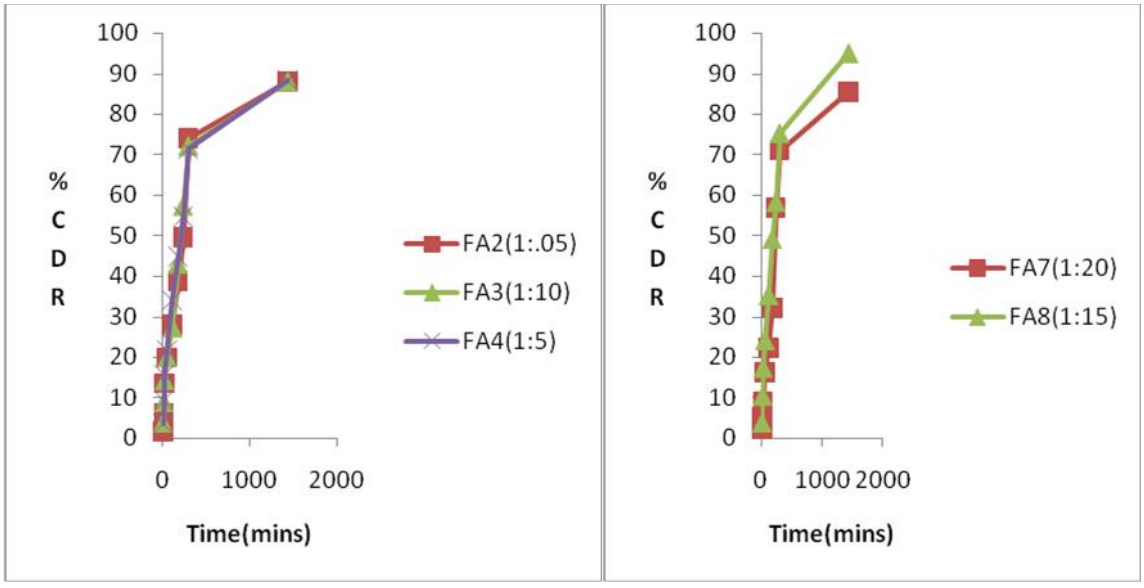


Fig4. *In-vitro* Release of chlorpromazine bio-nano formulations of almond bio polymer

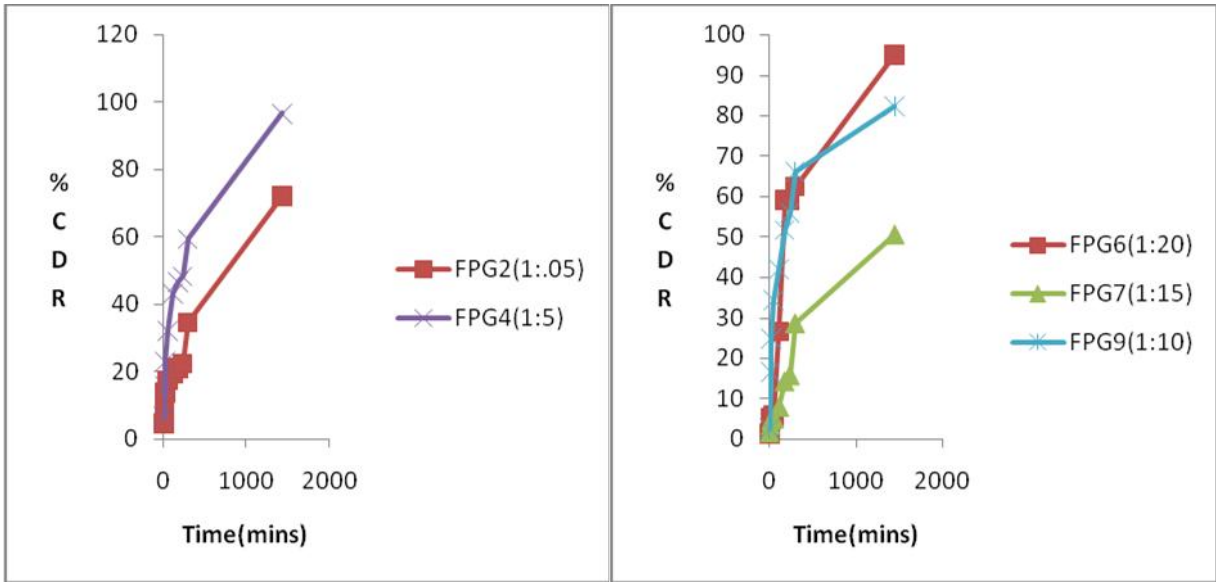


Fig5. *In-vitro* Release of chlorpromazine bio-nano formulations of Pullulan gum

Conclusion

Enhancement in drug delivery and absorption via a specific route of administration often becomes essential in the design of novel pharmaceutical products and new therapies. The pharmaceutical science and technology have progressed enormously in recent years, and that significant advances in therapeutics and an understanding of the need to optimize drug delivery in the body have brought about an increased awareness of the valuable role played by the dosage form in therapy. In turn, this has resulted in an increased sophistication and level of expertise in the design, development, manufacture, testing and regulation of drugs and dosage forms.The research work ensured that bio-polymer is safe and effective and can be used in the preparation of bio-nano particles. The isolated biomaterial was used as a novel material for the formulation of the bio-nanoparticles loaded with Chlorpromazine. Standard polymers pullulan gum was also used for the preparation of the standard formulations. The bio-nanoparticles were prepared by “Modified Non-Solvent Nano-precipitation Method”. It can be concluded that the biopolymer can be used for the preparation of NPs for nose to brain delivery as Pharmacokinetic study reveals that significant amount of drug reaches to the brain when administered intranasally and same was confirmed by observation as calmness in experimental animal. Delivery of API molecule to the brain for the management of depressive disorder is significant, minimizes the ADR by decreasing the dose and side effects of therapeutic molecule and offer good patient compliance through this novelistic approach.

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