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DEVELOPMENT AND PERFORMANCE EVALUATION OF CONTROLLED RELEASE OSMO-SINOSULES OF CHLORPROMAZINE HYDROCHLORIDE.

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ABSTRACT

The controlled release osmo-regulatory sinosules of chlorpromazine hydrochloride (Cpz.OR.CR) were prepared. Cpz.HCl granules containing, powdered sucrose (an osmogent) and soluble lactose were coated employing 12.5% w/v polybutylmethacrylate (PBMA) : polyvinylacetate (PVA) (80:20) solution containing varied quantity of channeling agent and plasticizer. At 10:1 core to coat ratio the prepared sinosules released the drug @ 6.50 mg/h following zero-order kinetics when tested for in vivo performance in Indian dogs and compared with conventional tablet Largactil® 25. The Cpz.OR.CR maintained uniform blood level around the peak level as compared with Largactil® 25 and resulted in significantly higher bioavailability of chlorpromazine.

INTRODUCTION

Chlorpromazine hydrochloride has attained an appreciable acceptance as an antipsychotic and antihistaminic agent and is widely used in the treatment and management of psychiatry. Rivera et al. (1) studied and established the mode and management of chlorpromazine in psychiatries. The chlorpromazine hydro-

chloride owing to short biological half life (5 hr) is administered in small dose (25 mg), 3 to 4 time a day inorder to maintain the therapeutic level (1,2). The developed different sustained and prolonged release preparations of chlorpromazine hydrochloride based on various principles have been studied for their potentialities in the management of psychiatry. Besides, patient compliance the products have been reported to be more therapeutically effective as the blood concentrations could be maintained at or around peak level for an extended period of time (3,4).

Sugerman and Rosen (5) studied the long acting chlorpromazine preparations for their absorption efficiency and urinary excretion profile. Goodman and Banker (6) described molecular level entrapment of drug as a precise method that could be used in controlling the release rate of drug(s). The method essentially based on the flocculation of primary amine containing drug(s) with anionic polymers.

Majority of the reports on controlled release, sustained release or prolong action dosage forms describe the use of synthetic polymers as dissolution modifiers of active agent(s) (7-11). The present work was an attempt to develop the controlled release osmo-regulated sinosules based oral system of chlorpromazine hydrochloride employing polybutyl methacrylate - poly vinyl acetate polymer coat as semipermeable lamina. Polybutyl methacrylate - polyvinyl acetate (80:20) composite mixture was identified to produce semipermeable films at thickness level (20-25 μm). Polyethlene glycol 4000 was used as channeling agent. To distribute the channeling agent uniformly a coating solution system w/o emulsion type was developed and used successfully.

EXPERIMENTAL

Materials

Chlorpromazine hydrochloride (May and Baker India, Ltd.), Butyl methacrylate monomer (E. Merck), Hydroquinone, Chloroform, Ethanol, Methanol (BDH Chemical Division Glaxo India, Ltd.), Benzoyl peroxide PEG-4000 (E. Merck). Largactil® 25 (May and Baker, India, Ltd.).

Polymerization of Butyl Methacrylate

Butyl methacrylate (BMA) monomer was polymerized employing bulk polymerization method (1,2). BMA monomer was dissolved in methanol to give 25% v/v solution. To 100 ml methanolic solution of monomer, benzoyl peroxide (200 mg) was added and dissolved with the help of shaking. The polymerization temperature was maintained at 50°C for 8 hr. At the termination of polymerization period, 0.50 g hydroquinone was added to inhibit further polymerization and polybutyl methacrylate was precipitated by the addition of distilled water. The precipitate was washed well with n-heptane, dried and rewashed with warm distilled water and finally vacuum dried at 45°C.

Determination of Average Molecular Weight

The solution of prepared PMBA was prepared in chloroform at 30°C in concentration range 0.1 - 0.7% w/v. The viscosity of prepared dilutions was determined and their specific viscosities were calculated. Using specific viscosity v/s concentration plots the intrinsic viscosities of polybutyl methacrylate was determined and used in the calculation of average molecular weight by employing published marck - Houwinks equation (12,13) $|n| = 2.50 \times 10^{-5} M^{0.74}$.

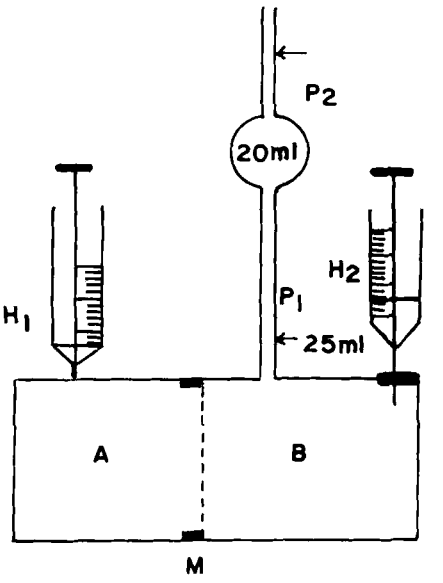

Figure 1

Designed Osmo meter. A and B are Compartments for distilled water and Osmogent-drug solution respectively H_1 and H_2 Hypodermic Syringe, P_1 Capillary P_2 Bulb to store the increased volume M- Semipermeable polymeric membrane.

Semipermeability Characteristics of Free Films

The semipermeability characteristics of polybutyl methacrylate free film and of the films that were prepared using PMBA and polyvinyl acetate (PVA) in various combinations was studied using a designed osmometer (Fig. 1). The polymeric films (20 μm thick) were casted on mercury substrates. To determine the semipermeability, the films were placed between two compartment i.e., A and B. Compartment A and B were filled with 25.0 ml of distilled water and 25 ml sodium chloride 2% w/v solution containing drug (100 μg/ml) respectively. After 24 hrs, on attainment of an equilibrium the increase in the volume of solution in compartment

TABLE 1

S. No.	Film composition	Thickness of film (um)	Increase in volume compar- tment B (ml)	Drug content in compartment B (ug/ml)
1	P.BMA (100)	20.00	6.50	99.50
2	P.BMA (100)	20.50	0.50	58.00
3*	P.BMA-PVA 80:20	19.50	10.80	98.00
4	P.BMA-PVA 60:40	20.00	8.50	80.00
5	P.BMA-PVA 40:60	19.50	7.60	82.50
6	P.BMA-PVA 20:80	20.00	7.00	74.00

P.BMA : Polybutyl methacrylate (2,30,000);
PVA : Polyvinyl acetone (2,00,000);
* : Selected composition of coating material.

B and the change in the drug concentration were determined and used as measure for permeability rating of film(s). The polymer composition that corresponds to the semipermeable film showing maximum permeability was selected for coating (Table 1).

Preparation and Coating at Cpz Granules

Weighed quantity of Cpz-HCl (75 g), powdered sucrose (75 g) and soluble lactose (75 g) were dry blended and wet granulated using 7.5% w/w (based on powder weight) alcoholic solution of PVP-40000. Resultant dump mass was passed through mesh no. 18 and dried at 40°C under vacuum. The granules were dry granulated and the mesh fraction 18/40 was used for coating. The solution of polybutyl methacrylate (mole. 2,30,000) and polyvinyl acetate (2,00,000) (80:20) in chloroform : methylene chloride (80:20) was emulsified with an aqueous solutions of PEG-4000 to prepare a w/o type of emulsion (5/95). The PEG was taken in various concentra-

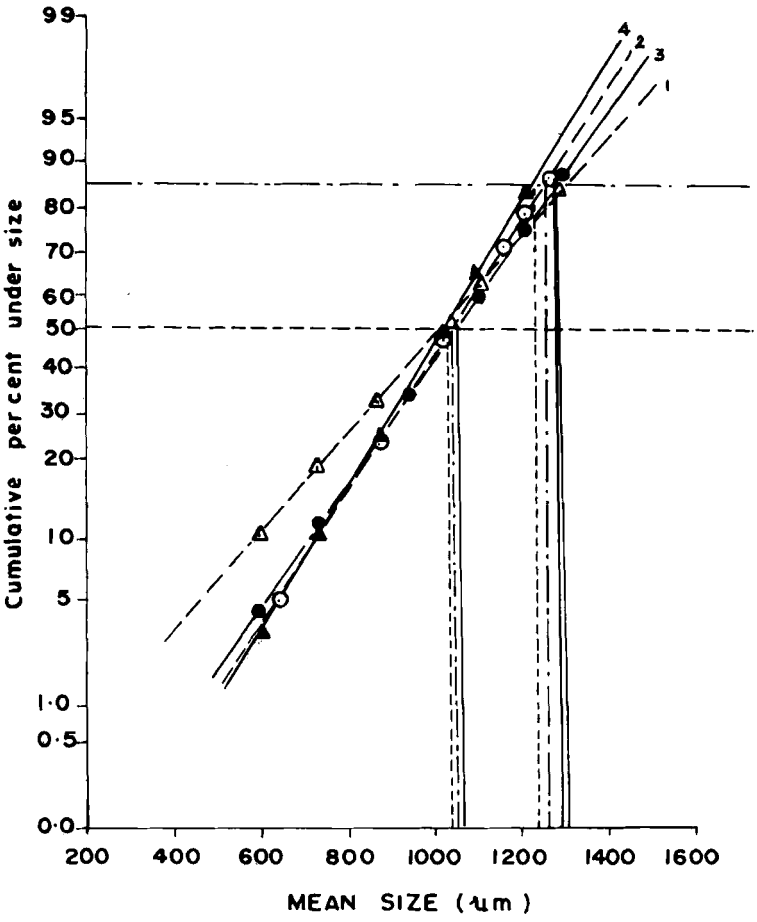

Figure 2

LOG PROBABILITY PLOT.
Cpz OR CR - 1; Cpz OR CR - 2;
Cpz OR CR - 3; Cpz OR CR - 4.

tions in aqueous phase i.e., 2.5, 5.0 and 7.5 w/w (based on polymer weight) to prepare different coating solutions.

For coating 500 g of granules were loaded in the coating chamber of Uni Glatt air suspension coating apparatus (Glatt. GmbH West Germany), and coated using 300 ml 12.5% polymer solu-

TABLE 2

Composition of Osmo-regulatory Cpz.HCl Controlled Release Products.

S. No.	Product	PEG content (% w/w)	Coating thickness (um)	Drug content (%)
1	Cpz.OR.CR-I	-	19.80	29.50
2	Cpz.OR.CR-II	2.5	20.40	30.10
3	Cpz.OR.CR-III	5.0	20.00	29.50
4	Cpz.OR.CR-IV	7.5	19.60	30.20

tion. The coating was accomplished by keeping inlet temperature 50°C outlet air temperature 38°C, spray pressure 25 psi and paristaltic pump speed at 8 rpm. The temperature of coating solution was maintained at 55°C during spray.

Determination of Coating Thickness

The average surface diameter of an individual coated granule was determined microscopically using a caliberated occular micrometer. About 200-250 granules of each products were observed and average size of granules in different size ranges was computed.

The cumulative under size was plotted as a function of diameter on a log probability scale (Fig. 2). The mean volume surface diameter (dvs) was then calculated using equations discussed and reported by Madam et al. (14) (Table 2).

Determination of Drug Content

The coated Cpz-HCl granules were powdered and accurately weighed (500 mg). To the powdered granules (500 mg), 10 ml chloroform was added to dissolve the coating material and drug

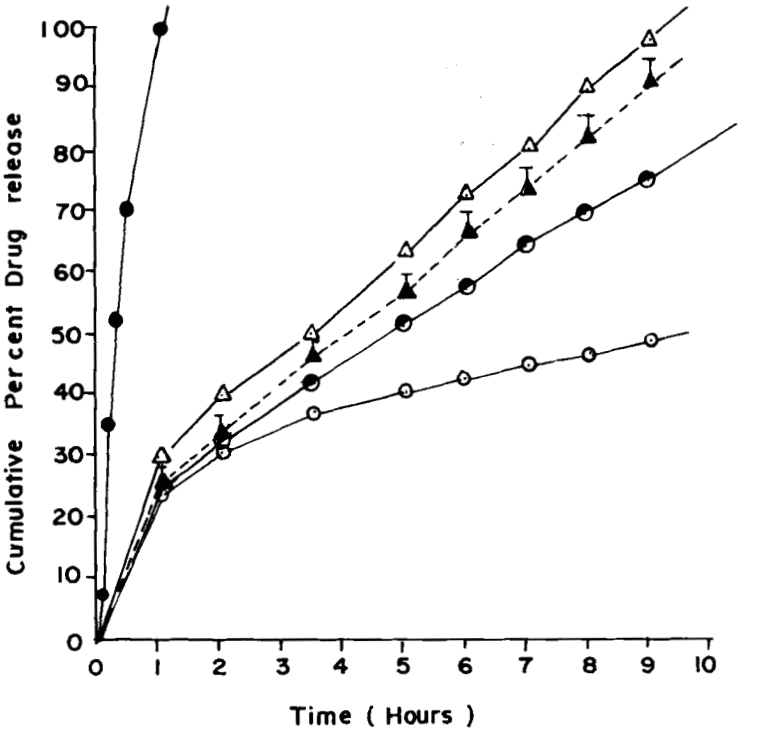

Figure 3

Percent Chlorpromazine hydrochloride release in in-vitro as a function of time. O—O Cpz.OR.CR-I; ●—● Cpz.OR.CR-II; ▲—▲ Cpz.OR.CR-III; △—△ Cpz.OR.CR-IV.

was extracted in 0.1N HCl and estimated spectrophotometrically at 254 nm using DB-G Beckman Spectrophotometer (15).

Dissolution Study

The coated Cpz.HCl granules (sinosules) were studied for in vitro dissolution using USP XX (16) dissolution test apparatus. Weighed quantity of Cpz.HCl granules was taken in the basket, and dissolution in gastrointestinal fluids of different pH (900 ml)

was determined following NF XIV (17) recommendations. The temperature and stirrer speed were maintained at 37°C and 100 rpm respectively. The aliquots of dissolution fluid withdrawn periodically were replaced with the fresh dissolution fluid of the same pH. Collected samples were analysed spectrophotometrically at 254 nm for their drug content. The dissolution pattern recorded for different products is shown in Fig. 3.

In Vivo Evaluation

Based on pharmacokinetics of drug (1,2) i.e. minimum effective concentration (MIC) 35-300 ng/ml elimination rate constant Ke, 0.1386 hr^{-1}, volume of distribution, 20 L/kg and using equation described by Robinson and Erikson (18) the calculated maintenance dose 75 mg equivalent to 254 mg Cpz.OS-CR III product and corrected initial dose 18.50 mg plain Cpz.HCl were filled in capsule (Cpz.OS.CR, capsules).

The absorption studies were carried out on ten Indian dogs weighing 10.5 to 11.0 kg divided in two groups (5 dogs in each).

The dogs following overnight fasting were weighed and anaesthetised with pentobarbitone sodium (30 mg/kg I.P. and maintenance dose of 5 mg/kg i.v. was administered when necessary). Initial blood samples prior to administration of formulations were collected then Largactil® 25 was given to dogs of one group while the dogs of another group were given Cpz.OS.CR Cap orally with 100 ml of water. After administration of Cpz.HCl formulations the blood samples were collected at an interval of 1 hr for 12 hr. Sterile normal saline solution 10 ml was infused prior to and after the blood sampling. The samples were centrifuged immediately and stored at freez temperature until analysed employing the method of Davis et al. (19) using a Hewlett Packard Model 5710A gas chromatograph with an electron capture detector.

RESULTS AND DISCUSSION

The osmometric study conducted on free films of polybutyl methacrylate (2,30,000) showed that films of 20 um thickness were selectively permeable to water while impermeable to drug, as total amount of drug in osmotic compartment B was remained unchanged whereas an increase in volume of solution was recorded. However, the permeability of solute (drug) molecules was limited. The film prepared with the blends of P.BMA and P.VA in various weight ratio were noted to be semipermeable only upto 20% w/w concentration of polyvinyl acetate in PBMA above which polyvinyl acetate noted to impart solute permeation possibly due to increased porosity in free films.

To provide uniform openings for the delivery of drug solution the channeling agent PEG 4000 was taken in aqueous phase (5 ml) and emulsified using span-80 (2.5 w/w) with 12.5 w/v solution (95 ml) of PBMA/PBMA-PVA in chloroform to form an emulsion (w/o). The coating solutions containing different concentrations of PEG in an aqueous phase were used to prepare different products using air suspension method. The products of almost the same coating thickness could be prepared and were studied for the in vitro release.

The in vitro dissolution profiles of chlorpromazine hydrochloride from different products are shown in Figure 3. The release from all the products except Cpz.OR.CR-I (coated without the channeling agent) followed zero order kinetics indicating that the release of drug was independent of pH. The osmotic pressure developed in granules core could be responsible for imparting the zero order release characteristics to the coated sinosules. Largactil 25 tablet released 100% drug within 1 hr.

The designed capsules containing Cpz.OR.Cr.I, II, III and IV when tested for in vitro dissolution released 33% of drug within

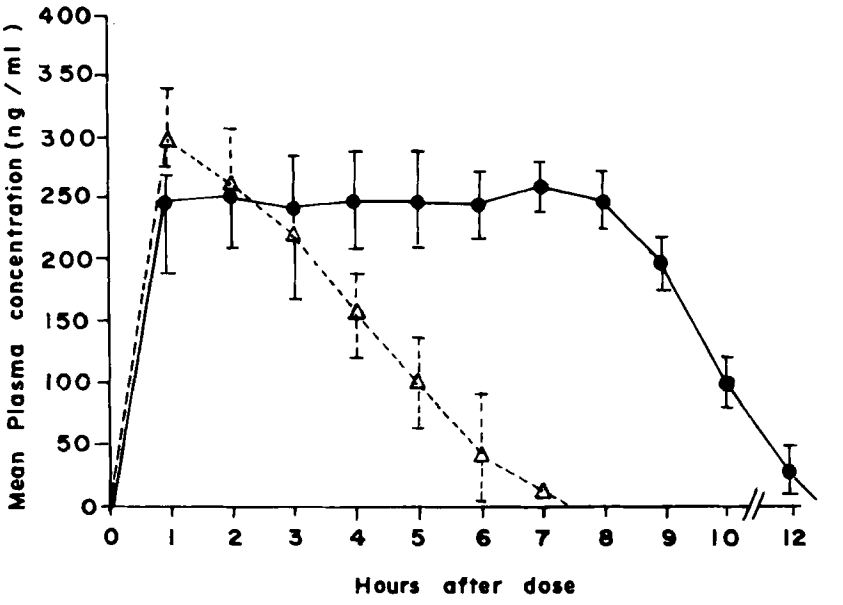

Figure 4

Mean (+ sE) Chlorpromazine plasma Concentration as function of time following oral administration of Cpz.OR sinosules & conventional tablet; Key: O O Cpz.OR CR-III and —●—●— Largactil®25 --Δ--Δ--.

1 hr which corresponds to the amount of incorporated initial dose (plain drug) and that released from the maintenance dose.

The coated granules released their drug content following zero order kinetics. The product Cpz.OR.CR.III which released the drug @ 6.50 mg/hr was selected for in vivo evaluation. The release pattern recorded for Largactil 25 was similar to the release of initial plain dose from Cpz.OR.CR-III capsules.

The mean Cpz plasma concentrations as function of time after oral administration of Largactil® 25 and Cpz.OR.CR-III capsules are shown in Figure 4. In order to study intersubject variation

TABLE 3

Derived Pharmacokinetic Parameters for Cpz.OR.CR Cap and Largactil 25 Treatments in Dogs.

S. No.	Treatment	t_{max} (hr)	C_{max} (mg/ml)	t_{lag} (hr)	AUC* $_{o-12}$ (mg/ml/hr)
1.	Largactil 25	1.00	300.00	Zero	1210.00
2.	Cpz.OR.CR-capsule	1.10	249.00	Zero	2084.75

*Calculated using trapezoidal rule.

the blood levels were normalized at C_{max} and other sampling times were made relative to this value. The data averaged in this way are shown along with standard deviations in Figure 4. The mean plasma levels produced in both the cases were significantly different from commencement to the attainment of peak levels ($p < 0.01$). After C_{max} the intersubject variation in the case of Cpz.OR.CR-III capsule was noted to be not significant ($p > 0.01$). This could be ascribed to the controlled disoolution of the drug during maintenance period. The C_{max} and t_{max} values recorded for Cpz.OR.CR-III capsule were not significantly different ($p > 0.01$) from Largactil®25. The comparative C_{max} and t_{max} obtained may be accounted for the release of initial plain drug from Cpz.OR.CR-III capsules at a rate comparable with Largactil 25. The AUC_{o--12} calculated for Cpz.OR.CR-III was significantly higher than Largactil 25 indicating higher availability of drug from controlled release product. The drug level was noted to remain around the peak level over an extended period of time, i.e. 12 hr. The derived pharmacokinetic parameters are shown in Table 3.

It is concluded that a proper mixture of polybutyl methacrylate and polyvinyl chloride (2,00,000) produced the film possessing semipermeable characteristics. Incorporation of PEG-4000 a channeling agent in the form of an emulsion into coating material and sucrose in core could lead to the successful preparation of osmoregulatory drug delivery system of Cpz.HCl, which hold promise for clinical studies.

REFERENCES

1. Rivera-Calimlin, L. Castendda and L.Lasegna, Clin. Pharmacol-Therap. 14, 978-86 (1973).
2. R.B. Cooper and G.M. Simpson, In "Psychopharmacology", Phenothiazines, Raven Press, New York, pp. 923-39, (1978).
3. J.C. Vasconcellos and A.A. Kurland, Dis. Nerv Sys. 19, 173 (1958).
4. L.E. Hollister, Curr. Ther. Res. 4, 471 (1962).
5. A.A. Sugerman and E. Rosen, Clin. Pharmacol. Therap. 5, 561 (1964).
6. H. Goodman and G.S. Banker, J. Pharm. Sci., 59, 1131 (1970).
7. S.C. Khanna and Speiser, J. Pharm. Sci., 59, 1398 (1970).
8. R.W. Crosswell and C.H. Backer, J. Pharm. Sci., 63, 440 (1974).
9. C.R. Willis and G.S. Banker, J. Pharm. Sci., 59, 1598 (1970).
10. B. Ferhadich, S. Borodkin and J.D. Buddenhagen, J. Pharm. Sci., 60, 209 (1971).
11. A. Malaiya and S.P. Vyas, J. Microencapsulation, 5, 243-253 (1988).
12. K. Othoner (ed.) "Encyclopedia of Chemical Technology" 2nd ed. vol. XIII, Interscience Publication, New York, London, pp. 341-348 (1967).
13. S. Kranse (ed.), "Dilute Solution Preparation of Acrylic and Methacrylic acid Polymers, special Product Dept. Bulletin, Sp 160, Rohm & Hass Philadelphia (1970).
14. P.L. Madam, L.A. Luzzi and J.C. Price, J. Pharm. Sci., 63, 280 (1974).
15. "British Pharmacopoeia", vol. II, Her Majesty's Stationary Office, Pharm. Press, London p. 748 (1980).

16. "The United States Pharmacopoeia" 20th rev. edn. Mac Publishing Co. Easton, PA (1980).

17. "The National Formulary", XIV edn., American Pharmaceutical Association, 77, Publication Washington, DC (1975).

18. J.R. Robinson and S.P. Eriksen, J. Pharm. Sci., 55, 1254 (1966).

19. C.M. Davis, C.J. Meyer and D.C. Fenimore, Clin. Chem. Acta, 78, 71-77 (1977).