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## Formulation and Evaluation of Trifluoperazine Hydrochloride Microcapsules

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Trifluoperazine hydrochloride (TFP) microcapsules were prepared by coacervation-phase separation technique using non-aqueous vehicles with ethyl cellulose (EC) as polymer. Coacervation was induced by solvent alteration technique followed by change in temperature. Microcapsules were prepared with different TFP-EC weight ratios. The prepared microcapsules were evaluated for various physico-chemical properties. The *in vitro* release studies indicated that the amount of drug release was decreasing with the increase in proportion of EC in the microcapsule and it followed a first order kinetics. The pharmacological studies indicated that the microcapsule might even reduce the drug induced extrapyramidal side effects (EPS). The pharmacokinetic studies revealed the maintenance of effective plasma concentration well below the toxic levels. Thus, the results indicated that the TFP loaded microcapsules might be a better alternative over conventional products.

Trifluoperazine hydrochloride is the most potent phenothiazine- antipsychotic compound and the continuous use of this drug entails a greater risk of inducing extrapyramidal side effects<sup>1</sup>. Review of literature has shown that low dose maintenance therapy of TFP is needed for prolonged psychiatric treatment with minimum occurrence of extra-pyramidal side effects<sup>2,3</sup>. Controlled release dosage form of TFP should be suitable for better therapeutic regimen mainly for its improved maintenance therapy in respect of reducing side effects and dosing frequency<sup>4</sup>. This novel dosage form makes possible the administration of 'old but effective drug in new form' i.e. re-patenting or reusing older, but effective drugs which might have been discarded because of certain inherent drawbacks. This controlled action drug delivery system can greatly improve the therapeutic profiles and safety of drugs by maintaining accurate spatial and temporal placement inside the body and by reducing the dosing frequency and dose quantity. On this hypothesis, it may be expected that TFP alone in controlled drug delivery system may improve its therapeutic profiles by preventing the occurrence of Parkinson's syndrome. The short plasma half-

life of TFP makes it an ideal candidate for controlled drug delivery<sup>5</sup>. A nylon microcapsule system of TFP was developed by Florence and others. This study and the other literatures suggested the feasibility of controlled release medication of TFP<sup>6,7</sup>. An attempt has been made in this study to develop ethyl cellulose based microcapsule system of TFP, keeping in view that TFP loaded microcapsules may alleviate the dose related problems and can reduce the frequency of multiple dosing and thereby improve patients' compliance.

### EXPERIMENTAL

TFP was obtained from Sun Pharma, Baroda and ethyl cellulose was supplied by Loba Chemicals, Mumbai as gift samples. All other chemicals used were of analytical grade and the reagents used for HPLC analysis were of HPLC grade.

#### Preparation of Microcapsules:

The microcapsules with the drug: polymer weight ratios of 1:1, 1:2, 1:3 and 1:4 (coded as TMC<sub>1</sub>, TMC<sub>2</sub>, TMC<sub>3</sub> and TMC<sub>4</sub>) were prepared by the solvent alteration method<sup>8-10</sup>. A 5% w/v solution of polyisobutylene in toluene was prepared by stirring at 500 rpm, using a

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mechanical stirrer, at 80°. The required quantity of ethyl cellulose was dissolved in it. To this solution, weighed amounts of TFP was added and dispersed. The mixture was then gradually cooled to room temperature (20°) and petroleum ether was added drop wise. The addition of petroleum ether caused the precipitation of ethyl cellulose and resulted in the formation of a cocervate of ethyl cellulose around TFP. After 1 h of constant stirring, the formed microcapsules were isolated by decantation of the supernatant liquid. The isolated microcapsules were washed with chilled (5°) petroleum ether for 5 times and separated by vacuum filtration. It was air dried at room temperature (20°) for 5 h and preserved in an airtight dessicator until further use.

The TFP microcapsule, thus prepared, was subjected to different evaluations in order to its suitability as a dosage form. These include-

#### **Determination of particle size:**

Particle size of drug-loaded microcapsules can affect the flow characteristics and proper mixing during formulations. The particle sizes of the prepared microcapsules were determined by employing a method of sieving. Sieves were arranged serially (sizes were 200/240, 240/300, 300/350, 350/400 and 400/450) one on top of another, so that the top most sieve was with the largest opening and the bottom most sieve having the smallest. A known weight of the microcapsules was placed on the top most sieve and the sieves were shaken for 3 min. The microcapsule that passes through one sieve but retained on the next finer sieve was collected, weighed and the average was determined. The maximum amounts retained in the specific sieves (200/240 and 400/450) were taken for optical microscopy.

#### **Determination of flow properties:**

The flow properties of the microcapsules were determined with respect to their angle of repose. Fixed funnel method was employed for finding the angle of repose.

#### **Determination of bulk density:**

A known weight of the microcapsules were taken in a measuring cylinder and the cylinder was tapped on a hard surface 3 times from a height of 1 inch at 2 seconds interval between the tappings. The bulk density was determined by using the following formula:

$$\text{Bulk density} = \text{mass/bulk volume}$$

#### **Determination of drug content :**

Microcapsules equivalent to 100 mg of TFP was crushed and triturated with 50 ml of 0.1 N HCl. The mixture was transferred to a 100 ml standard volumetric flask and the volume was adjusted with 0.1 N HCl. The flask was then shaken for 12 h using a mechanical shaker. After shaking, the solution was filtered and the filtrate was diluted appropriately with 0.1 N HCl and the concentration was determined using a UV spectrophotometer (Shimadzu (UV-160-A) at 256 nm.

#### **FTIR spectroscopy :**

This is the precise study for the interaction of drug with polymer. The FTIR spectra of pure TFP, pure ethyl cellulose and the microcapsules were recorded using a FTIR spectrophotometer (Perkin-Elmer) by KBr disc method. Fifty milligrams of sample and 150 mg of potassium bromide were taken in a mortar and triturated. The triturated sample was placed in a pellet maker and compressed at 10 kg/cm<sup>2</sup> using a hydraulic press. The pellet was kept into a sample holder and scanned from 400 to 4000 cm<sup>-1</sup>.

#### **In vitro dissolution studies :**

The dissolution studies were carried out on TFP microcapsules using the U.S.P. (XXIII) paddle method with 900 ml of freshly prepared 0.1 N HCl as the dissolution medium. The U.S.P. employed 0.1 N HCl for TFP tablet dissolution medium and thereby this test was carried out accordingly. A certain amount of each sample corresponding to 50 mg of TFP was sprinkled on the dissolution medium equilibrated to 37±1°. The paddle was rotated at 50 rpm and 2 ml samples of the solution were withdrawn at appropriate time intervals. The concentrations of TFP were determined by using UV spectrophotometer at 256 nm after appropriate dilutions. The volume of the dissolution medium was kept constant throughout the dissolution run, by adding the same volume of the fresh medium after each sample was withdrawn.

#### **Pharmacological studies :**

The degree of TFP-induced catatonia (Extra pyramidal side effects) was studied in albino rats<sup>11</sup>. Twelve-hour fasting rats (200-225g) were divided into 4 groups, consisting of 3 animals per group. The various formulations (pure drug, innovator's product of TFP and TMC<sub>2</sub>) were

administered orally, once at a time in the dose of 2.7 mg/kg. All the formulations were suspended in 0.5% w/v carboxy methyl cellulose (CMC) solution and immediately administered. Group I-Received only 0.5% CMC suspension (1ml/kg body weight) and served as the solvent control. Group II-Received the pure drug suspended in 0.5% CMC solution. Group III-Received the innovator's product for TFP suspended in 0.5% CMC solution and Group IV-Received the formulated microcapsules (TMC<sub>2</sub>) suspended in 0.5% CMC solution.

After administering the formulations, the degree of catatonic response was observed at predetermined time intervals for 72 h. Depending upon the observations, different scores were assigned as stage I-rats move normally when placed on the table score = 0, stage II-rats move only when touched or pushed-score=0.5 stage III-rats move on the table with front paws set alternatively on a 3cm high block, fails to correct the posture within 10 seconds, score 0.5 for each with a total score of 1 for this stage and finally stage IV-rats fail to remove the paws when the front paws placed alternatively on 9 cm block, score = 1 for each with a total score of 2 for the stage.

Thus, for a single rat, the maximum possible score would be 3.5, revealing total catatonia.

#### ***In vivo* pharmacokinetic study :**

Nine, healthy Newzealand white rabbits (6 males and 3 females) each weighing 1.5-2.5 kg were used in this study. They were divided into 3 groups, each consisting of 3 rabbits (2 males and 1 female). Group A-received the pure drug, group B-received the innovator's product for TFP and group C-received the formulated microcapsule (TMC<sub>2</sub>). The dose of TFP drug powder was 0.93 mg/kg or equivalent. All the formulations were suspended in 0.5% w/v CMC solution and administered immediately following an overnight fast of 12 h. The doses of the formulations to be administered were determined as per the body weights of the individual animals. Immediately after the administration of the formulation, 2.5 ml of blood samples were withdrawn from the marginal ear vein of the corresponding rabbits and transferred into a heparinized glass centrifuge tube and centrifuged immediately (3000 rpm for 15 min). The plasma was separated and stored at 10°. This was considered as the blank. Subsequently, the same volumes of blood were withdrawn from the marginal ear vein of the corresponding rabbits

and the corresponding plasma was separated and stored as mentioned until further use.

#### **Extraction of TFP from plasma :**

Half a millilitre of plasma was transferred into a 10 ml standard flask. To this, 100 ng/ml of trihexyphenidyl HCl (internal standard) was spiked. To this solution, 1 ml of acetonitrile was added, shaken for 5 min and centrifuged at 5000 rpm for 15 min. The supernatant layer was separated, transferred into a 10 ml standard flask and diluted with a mixture of acetonitrile and 50 mM phosphate buffer (pH 4.5) in the ratio of 80:20 (mobile phase). The resulting solution was analyzed using HPLC.

#### **Chromatographic conditions :**

Water's HPLC system was used. The column used was Zorbax® C8 (5 µ, 25 cm x 4.6 mm, id). A mixture of acetonitrile and 50 mM phosphate buffer (pH 4.5) in the ratio of 80:20 was used as the mobile phase at a flow rate of 1.5 ml/min with an operating pressure of 3000 psig. A Rheodyne® 7125 injector with a 20 µl loop was used for injecting the samples. TFP was detected at 256 nm with a sensitivity of 0.005 AUFS. The separation was carried out at room temperature (20°).

## **RESULTS AND DISCUSSION**

The various properties of the formulated microcapsules are depicted in table-1. A combination of these properties determines the behaviour of bulk materials. The flow properties of solids have great impact on the encapsulation process for dosage form from manufacturing which requires the flow of granular materials, from a storage container to filling section, mixing and demixing of granules. Once again, flow characteristics are influenced by particle size, shape of particles and as well bulk density. The particle sizes of the microcapsules were within the size range of 26.9-64.2 µ. The increase in the particle size of the microcapsules could be attributed to the increase in the proportion of ethyl cellulose. The bulk densities of the microcapsules were in between 0.35-0.78 g/ml with good flow characteristics, having the angle of repose (Q) between 18-20°. The drug loading of the various batches of the microcapsules varied between 56-84%. The FTIR spectral data of microcapsules loaded with drug were almost in agreement with that of pure EC, clearly indicates that there was no interaction between the drug molecules and the coated polymer employed in microcapsule preparations. The FTIR data obtained from

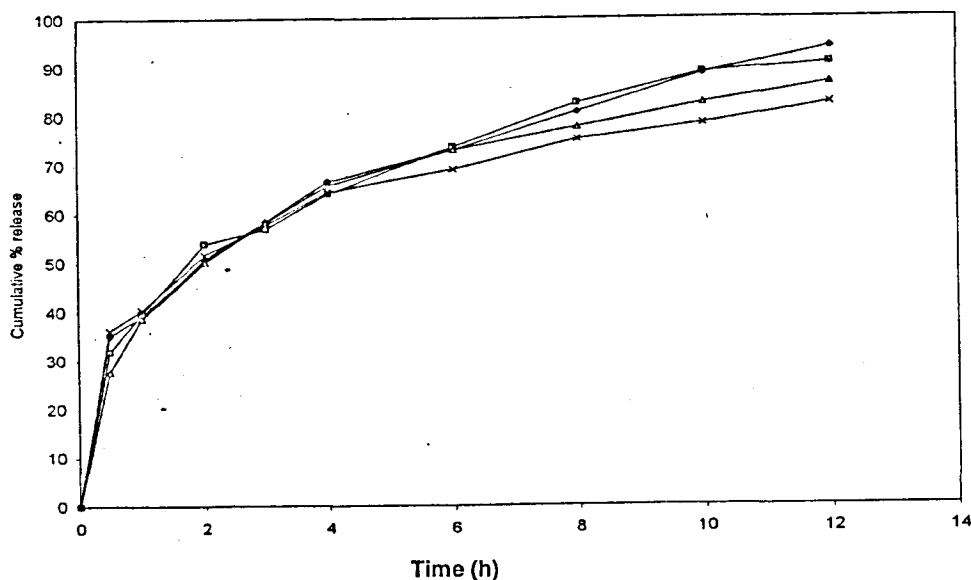


Fig. 1 : Dissolution of TFP Microcapsules. Drug release was found 94% for TMC<sub>1</sub> (-♦-), 90.7% for TMC<sub>2</sub> (-□-), 86.7% for TMC<sub>3</sub> (-Δ-) and 82.5% for TMC<sub>4</sub> (-x-) after 12 h of study

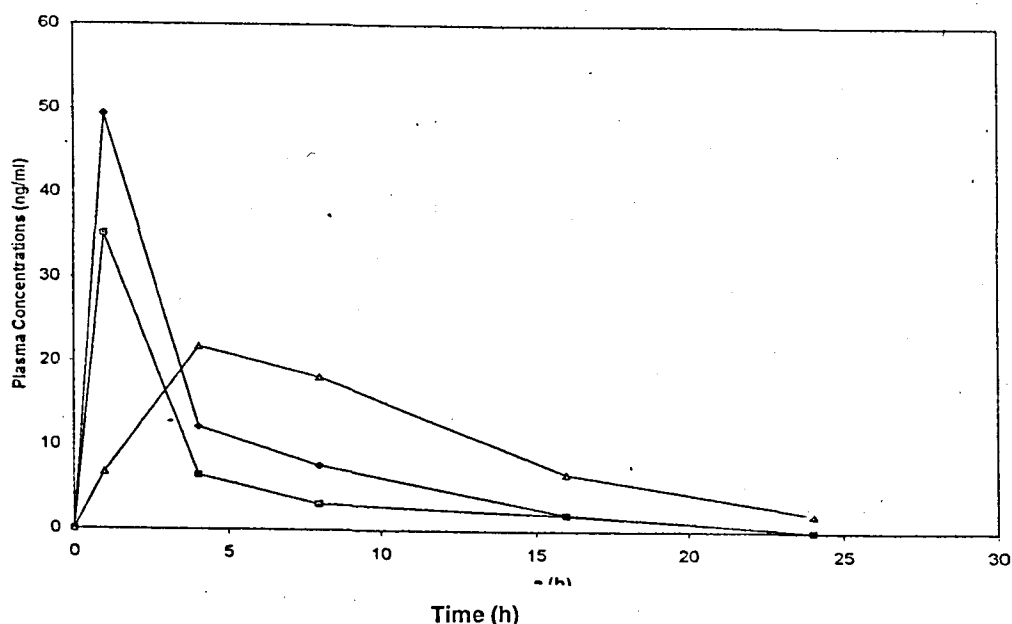


Fig. 2 : Plasma levels of TFP in rabbits.  $C_{max}$  for TFP powder (-♦-) was 49.4 ng/ml, for innovator's product (-□-) was 35 ng/ml but for TMC<sub>2</sub> (-Δ-) was most effective plasma concentration of 21.7 ng/ml during 24 h study period.

the solvent extract of microcapsules showed the presence of drug molecule and thereby it was confirmed that the drug molecules had been entrapped with the polymer films. The *in vitro* dissolution profiles of the various batches of the microcapsules are shown in figure 1. The *in vitro* dissolution studies revealed that the release of the drug from the microcapsules was sustaining in nature with a maximum drug release of 94% during 12 h.

The dissolution studies also revealed that the drug release was retarded as the concentration of ethyl cellulose increased in the microcapsules. This could be attributed to the hydrophobic nature of ethyl cellulose. The dissolution study was carried out only in acidic pH because of the drug, TFP solubility and as per pre-requisite for U.S.P. dissolution test media. The drug release was steady with almost 50% drug was released within 2h and

TABLE 1 - PROPERTIES OF THE FORMULATED MICROCAPSULES

Formulation Code	Drug-polymer ratio	Mean diameter ( $\mu\text{m}$ )	Bulk Density (g/cc)	Angle of repose ( $^\circ$ )	Drug Loading (%)
TMC <sub>1</sub>	1:1	26.99	0.61	20 $^\circ$ .27'	56.0
TMC <sub>2</sub>	1:2	31.56	0.51	18 $^\circ$ .20'	83.9
TMC <sub>3</sub>	1:3	43.07	0.35	20 $^\circ$ .20'	68.0
TMC <sub>4</sub>	1:4	64.21	0.78	20 $^\circ$ .44'	72.5

TABLE 2 - CATATONIC STUDY FOR THE VARIOUS TFP FORMULATIONS

Formulation	Max. Score (out of 3.5)	Onset of response (h)	Duration of max. score (h)	Remarks
TFP Powder	3.5	2	2	Max. score within a short span of time
Innovator's product of TFP	3.5	6	2	Max. score within reasonable time
TMC <sub>2</sub>	1.5	4	16	Less score, fast onset but persisted for a long time

remaining drug was released in sustaining fashion for a period of 12h. The drug released was declined exponentially thereafter confirmed the monolithic system of microcapsules. From the graphs, it can be concluded that the release followed the first order kinetics.

Based on the *in vitro* dissolution data and the drug loading efficiency TMC<sub>2</sub> was selected for the pharmacological and the pharmacokinetic studies. The catatonic scores of the pure drug, the innovator's product and TMC<sub>2</sub> are depicted in table-2. This study, on albino rats, gave an indication that the formulated microcapsules could improve the therapeutic profile of TFP, as the maximum catatonic score of the microcapsule was found to be 1.5 when compared to the pure drug and the innovator's product (score maximized to 3.5). This result indicated that the formulated microcapsule might not lead to drug induced EPS. The mean concentration of TFP from various formulations in rabbit's plasma are given in figure-2. The pharmacokinetic study revealed that the  $C_{\text{max}}$ ,  $t_{\text{max}}$ ,  $K_e$ , and  $f_{\text{rel}}$  for TMC<sub>2</sub> was 21.7 ng/ml, 4 h, 0.117 h<sup>-1</sup> and 159.1% respectively, where as for the innovator's product, they were 35 ng/ml, 1 h, 0.1 h<sup>-1</sup> and 61.1% and for

the pure drug, they were 49.4 ng/ml, 1 h, 0.2 h<sup>-1</sup> and 100%. The value of AUC<sub>0-24</sub> for TMC<sub>2</sub> was 282.5 ng/ml/h as against 108.7 and 177.6 ng/ml/h for the innovator's product and the pure drug respectively. The pharmacokinetic study thus revealed that the duration of the effective plasma concentration of TFP from the formulated microcapsule was around 16 h without showing toxic levels as against the innovator's product and the pure drug. The bioavailability of TFP from microcapsules dosage form is better than the authentic drug or conventional dosage forms may be due to avoiding chemical degradation in the stomach or more resistant to pre-systemic metabolism in the gut, gut wall or liver. This improved bioavailability may also be due to avoiding pre-absorptive metabolism by enzymes in the proximal small intestine or bacteria in the distal small intestine and colon.

Therefore, it can be concluded that the TFP microcapsule may reduce the occurrence of the degree of EPS, keeping its optimum therapeutic efficacy and thus could be considered as a better alternative over the conventional dosage forms.

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