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FORMULATION AND EVALUATION OF MICROCAPSULES OF TRIHEXYPHENIDYLE HYDROCHLORIDE BY SOLVENT EVAPORATION METHOD.

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ABSTRACT

Trihexyphenidyle is a lipophilic antiparkinsonian drug with short half life. Practically slightly soluble in water makes formulation and delivery difficult. By formulating the same in the microcapsule by using biodegradable polymer Eudrajit L 100 and S 100, the half life and solubility can be altered and hence drug release pattern. Trihexyphenidyle microcapsules were prepared by solvent evaporation method by using different drug-polymer ratio (1:2, 1:3, 1:4, 1:5). Prepared microcapsules were evaluated for the particle size, percentage yield, incorporation efficiency, flow property and *in vitro* drug release at pH 6.8 for 12 hours. From the result we can conclude that as the concentration of polymer increases, it affects the particle size, percentage yield and drug release of micro capsules. The formulation F2 shows the excellent flow properties, particle size, percentage yield (91.24%), incorporation efficiency (94.59%) and percentage drug release (95.88%) for a period of 12 hrs. Results of the present study indicate that Trihexyphenidyle microcapsules can be successfully designed to develop sustained drug delivery, that reduces the dosing frequency and their by we can increase the patient compliance.

INTRODUCTION: Conventional oral drug administration does not usually provide rate-controlled release or target specificity. In many cases, conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration. In order to obtain maximum therapeutic efficacy, it becomes necessary to deliver an agent to the target tissue in the optimal amount for the required period of time, thereby causing little toxicity and minimal side effects [1].

Desired drug release can be provided by rate-controlling membranes or by implanted biodegradable polymers containing dispersed medication. Microparticulate drug delivery systems are considered and accepted as a reliable one to deliver the drug to the target site with specificity, to maintain the desired concentration at the site of interest without untoward effects [2].

Microencapsulation is a useful method which, prolongs the duration of drug effect significantly and improves patient compliance. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained [3].

Parkinson's disease is the most common neurodegenerative movement disorder of the brain that leads to shaking (tremors) and difficulty with walking, movement, and coordination, which affects about 1% of the population over age 60 . Sometimes Parkinson's disease occurs in younger adults.

It affects both men and women. Nerve cells use a brain chemical called dopamine to help control muscle movement. Parkinson's disease occurs when the nerve cells in the brain that make dopamine are slowly destroyed. Without dopamine, the nerve cells in that part of the brain cannot properly send messages. This leads to the loss of muscle function. The damage gets worse with time.

Trihexyphenidyle is also known as benzhexol, is an Anti- Parkinsonian agent of the antimuscarinic class. It binds to the M_1-muscarinic receptor and possibly the dopamine receptor and by that trihexyphenidyl blocks efferent impulses in parasympathetically innervated structures like smooth muscles (spasmolytic activity), salivary glands, and eyes (mydriasis). Trihexyphenidyl is rapidly absorbed from the gastrointestinal tract. After oral administration, the onset of action occurs within 1 hour, peak effects last 2 to 3 hours. Half life of the drug is 3.3-4.1 hours and in order to maintain therapeutic plasma levels, the drug must be administered approximately 2-5mg daily by oral individual dosage.

Microencapsulation is defined as the application of a thin coating to individual core materials that have an arbitrary particle size range between 5 and 5000 μm[4]. Microencapsulation is widely used in the pharmaceutical and other sciences to mask tastes or odors, prolong release, impart stability to drug molecules, improve bioavailability, and as multi-particulate dosage forms to produce controlled or targeted drug delivery [5, 6, 7, 8]. It is therefore, a rapidly expanding technology for achieving sustained-release dosage forms.

The solvent- evaporation method of micro-encapsulation involves the use of emulsification of a solution containing polymer and drug with an additional medium in which the drug and polymer cannot dissolve [9]. The technique is relatively simple and has been used to prepare microcapsules of a variety of compounds using several different polymeric materials [6, 10].

The aim of this work was to develop microcapsules of Trihexyphenidyl by solvent evaporation technique. Due to physicochemical properties and short half life, Trihexyphenidyl is a suitable candidate for Antiparkinson treatment.

MATERIALS: Trihexyphenidyle was obtained as a gift sample from the Stadmed Pvt. Ltd. Kolkata. pH sensitive methacrylic acid co-polymers (Eudragit® L-100 and S- 100) were supplied as gift sample by Yarrow Chem. India ltd., Heavy liquid paraffin, petroleum ether was obtained from S.D. fine Chem. Ltd., Mumbai (India), Span 80 were supplied from Rolex chemicals ltd , Mumbai. Acetone was supplied from Suvidhinath laboratories, Baroda All other chemicals and reagent used in this study were of analytical grade.

METHOD [11]: Microcapsules were prepared by solvent evaporation method. Accurately weighted Eudragit L-100 and S-100 in different ratios were dissolved in 20ml of acetone to form a homogenous polymers solution. Core material, i.e., Trihexyphenidyl was dispersed in it and mixed thoroughly (**Table 1**). This organic phase was slowly poured at 15°C into liquid paraffin (100 ml) containing 1% (w/w) of Span-80 with stirring at 1000 rpm to form a uniform emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microcapsules were formed. The microcapsules were collected by decantation and the product was washed with petroleum ether (40-60°C), four times and dried at room temperature for 3 hrs. The microcapsules were then stored in a desiccators over fused calcium chloride.

TABLE 1: FORMULATION OF TRIHEXYPHENIDYL MICROCAPSULES

INGREDIENTS	F1	F2	F3	F4
Eudragit L 100 (mg)	50	50	50	50
Eudragit S 100 (mg)	100	150	200	250
Trihexyphenidyl (mg)	100	100	100	100
Acetone (ml)	20	20	20	20

Evaluation of Flurbiprofen Microcapsules:

Percentage Yield [12]: The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microcapsule.

% yield = (Actual weight of product / Total weight of excipient and drug) x 100

Incorporation Efficiency [11, 13]: In 100ml volumetric flask 25mg of crushed microcapsules were taken and dissolved with small quantity of ethanol of the volume is made up to mark with pH 6.8 and stirred for 12 hours. After stirring the solution was filtered through Whatman filter paper and from the filtrate appropriate dilutions were made and absorbance was measured at 206 nm by using UV- spectrophotometer 1800 (Shimadzu).

Micromeritic Properties [14, 15]:

Particle Size: Determination of average particle size of the Trihexyphenidyl microcapsules was carried out by the optical microscopy method. A minute quantity of microcapsules were dispersed in glycerin and then spread on clean glass slide and average sizes of 100 microcapsules were determined in each batch.

Angle of Repose: Determination of angle of repose Trihexyphenidyl microcapsules were carried out by employing fixed funnel method.

$$\text{Angle of repose } \theta = \tan^{-1} (H/R)$$

Where, H = Height of the pile; R = Radius of the pile

Scanning Electron Microscopy [16]: The samples for SEM analysis were prepared by following method. The shape and surface morphology of the microcapsules was studied by using scanning electron microscope (Materials Research Centre, Indian Institute of Science (IISc), Bangalore - 560012, INDIA). Microcapsules were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 mm of Hg). The microcapsules were viewed at an accelerating voltage of 10KV.

Drug Release [16-19]: *In vitro* release studies: *In vitro* dissolution profile of each formulation was determined by employing g USP XXII type 2 basket method (900 ml of pH 6.8-phosphate buffer, 100 rpm, 37±0.5^{o}C). Microcapsules equivalent to 100 mg of Trihexyphenidyl was loaded into the basket of the dissolution apparatus. Aliquot of 5 mL was withdrawn from the dissolution media at suitable time intervals and the withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ_{max} 206 nm after suitable dilution if necessary, using phosphate buffer of pH 6.8 as blank. Results of in vitro drug release studies obtained from absorbance data were tabulated and shown graphically as Cumulative % drug released Vs Time.

RESULT AND CONCLUSION:

Preparative aspects of Eudragit microcapsules: Above formulated preparation remains un-disintegrated at pH less than 6 and it releases the drug slowly at pH above 6 i.e., in the intestine. Hence the prepared microcapsules of Trihexyphenidyle shows improved half life. To prepare pH dependent microcapsules the O/O (oil in oil) emulsion solvent evaporation technique was used since it yields more uniform particles. The method is correctly referred as O/O instead of W/O (water in oil) since a polymeric solution in organic solvent is considered as oil in micro encapsulation terminology. The use of span 80 as an emulsifying agent decreased the interfacial tension between the lipophilic and hydrophilic phases of the emulsion and further simplified the formation of microcapsules.

Span 80 formed a thin film around the droplets and thereby reduced the extent of coalescence, before hardening of the capsules, on collision of the droplets. The resultant microcapsules were free-flowing, and the use of span 80 was deemed effective. When 1:1 (w/w) drug/polymer concentrations were used for both the Eudragit RS and RL polymers, the quality of microcapsules formed was poor (**Figures 2 and 3**). These were irregularly shaped, not free flowing, and presented with lots of indentation. Microcapsules were only formed when the polymer concentration was increased to ratios of between 1:2 and 1:4 (w/w) with respect to the drug concentration.

Discrete, spherical, and uniform microcapsules were obtained with a 1:2 (w/w) drug/polymer ratio for both the RS and RL polymers, as can be seen in Figures 2-5. It is also evident that the microcapsules exhibited slightly porous surfaces, probably due to the high concentration of drug in the microcapsules. Liquid paraffin was selected as a continuous phase, since

Trihexyphenidyl and Eudragit RS/RL are only very slightly soluble in liquid paraffin. Acetone has a dielectric constant of 20.7 and was therefore chosen as the dispersed or inner phase, since solvents with dielectric constants between 10 and 40 showed poor miscibility with liquid paraffin [20, 21, 22].

Petroleum ether or n-hexeane was used to clean the microparticles since it removes liquid paraffin without affecting the integrity of the microparticles.

Yield of Microcapsules: Results are shown in **Table 2**. The drug content was found to be very high in all the cases probably due to polymer loss by adherence to the container as a result of viscous nature of slurry.

Incorporation Efficiency: The incorporation efficiency of microcapsule formulation F1 to F4 varied from 88.25% ± 0.85 to 70.89% ± 0.78 (as shown in **table 2**). The incorporation efficiency was found to be good in all formulations.

TABLE 2: PERCENTAGE YIELD AND INCORPORATION EFFICIENCY OF TRIHEXYPHENIDYLE MICROCAPSULES

Formulation code	Percentage yield	Incorporation efficiency
F1	86.41± 0.37	88.25± 0.85
F2	91.24± 0.50	94.59±0.68
F3	84.20± 0.080	81.50± 0.50
F4	82.85± 0.39	70.89± 0.78

All values are represented as mean ± standard deviation (n=3)

Micromeritic properties: The arithmetic mean particle size of the formulations was determined by the optical microscope fitted with an ocular micrometer and stage micrometer. The average mean particle sizes of the microcapsules were found to be 368.32 ± 1.01, 362.58 ± 1.14, 395.57 ± 2.5 & 435.84 ± 1.5 (as shown in **table 3**).

For formulations F1, F2, F3 and F4 respectively, the mean particle size of the microcapsules significantly increased with increase in polymer concentration due to high viscosity of medium at a higher polymer concentration resulting in enhanced interfacial tension and diminished shearing efficiency. The angle of repose of microcapsule ranges from 17°55” ± 1.83, 18°35” ± 3.85, 21°40” ± 2.75 and 23°70” ± 3.35 (as shown in **table 3**). The values of angles of repose indicate excellent flow properties.

TABLE 3: MICROMERITIC PROPERTIES OF TRIHEXYPHENIDYLE MICROCAPSULES

Formulation code	Particle size (µm)	Angle of repose
F1	368.32± 1.01	$17^{O}55$” ± 1.83
F2	362.58± 1.14	$18^{O}35$” ± 3.85
F3	395.57± 2.5	$21^{O}40$” ± 2.75
F4	435.84± 1.5	$23^{O}70$” ± 3.35

Scanning Electron Microscopy (SEM): Morphology of microcapsules was examined by scanning electron microscopy. The view of the microcapsules showed smooth surface morphology exhibited range of sizes within each batch (as shown in **fig. 1-4**). The outer surface of microcapsules was smooth and dense, while the internal surface was porous. The shell of microcapsules also showed some porous structure due to evaporation of solvent entrapped within the shell of microcapsules after forming smooth and dense layer.

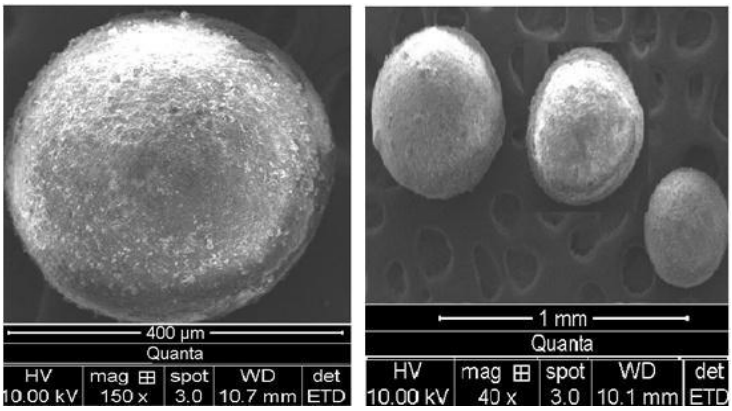

FIG. 1: SCANNING ELECTRON MICROSCOPY (SEM)

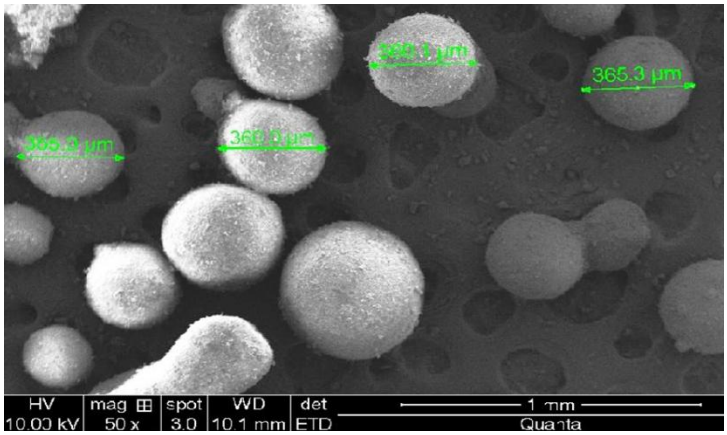

FIG. 2: SCANNING ELECTRON MICROSCOPY OF FORMULATION F2

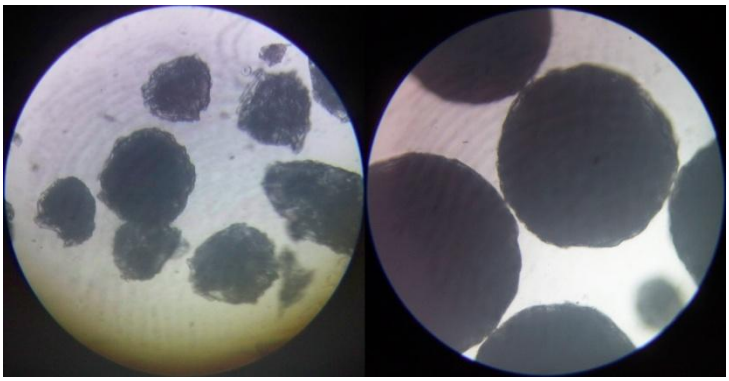

FIG. 3: MICROSCOPIC EVALUATION OF PREPARED MICROCAPSULES F1 & F2 RESPECTIVELY

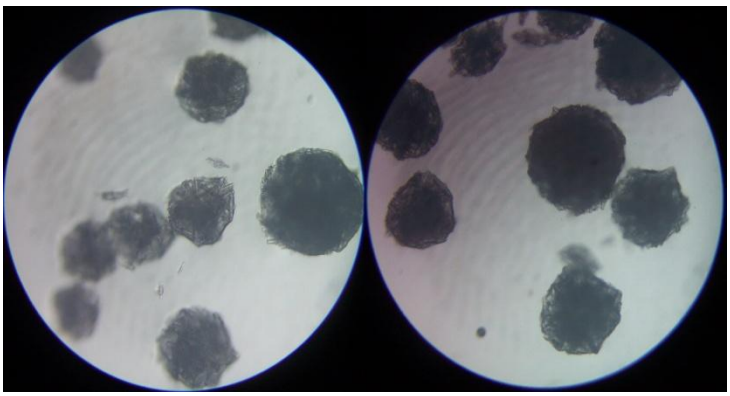

FIG. 4: MICROSCOPIC EVALUATION OF PREPARED MICROCAPSULES F3 & F4 RESPECTIVELY

Drug release: *In vitro* release studies were carried out using USP XXII type 2 basket assembly. The release profile obtained for all the four formulations were shown in **Fig. 5**. It is important to note that the dissolution behavior of granules and powders is greatly influenced by their wettability, surface area, and particle size distribution [23]. Drug release from microcapsules should theoretically be slower as the amount of polymer is increased because of an increase in the path length through which the drug has to diffuse. It was observed that the drug release from the formulations decreased with increase in the concentration of polymer added in each formulation.

The release of drug from polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increase the time required to swell also increase thereby decrease in the drug release. However, the release showed a bi-phasic release with an initial burst effect. In the first 30 min drug release was 25.5%, 21.5%, 20.5% and 19.9% for F1, F2, F3 and F4, respectively.

The mechanism for the burst release can be attributed to the drug loaded on the microcapsule or imperfect entrapment of drug. The overall cumulative % release for F1, F2, F3 and F4, were found to be 94.3%, 97.5%, 88.8%, and 83.67% at the end of 12th hour.

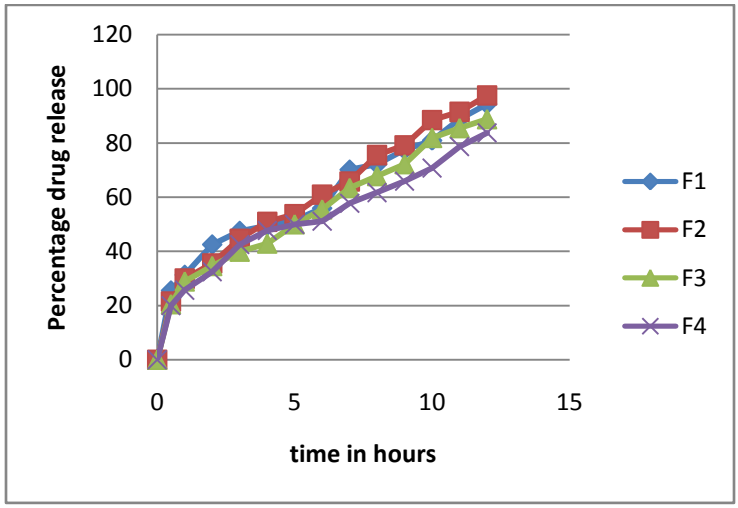

FIG. 1: *IN-VITRO* DRUG RELEASE PROFILE OF TRIHEXYPHENIDYL MICROCAPSULE FORMULATION F1 TO F4

CONCLUSION: The solvent-evaporation method using Eudragit polymers at optimum levels was effective for the formation of Trihexyphenidyl microcapsules. From the results it seems that formulation F2 was found to be satisfactory in terms of excellent micromeritic properties, yield of microcapsule, (91.24%), incorporation efficiency (94.59%) and highest in vitro drug release of 97.5% in a sustained manner with constant fashion over extended period of time for 12 hrs. So from the result, we can conclude that concentration of polymers affect all the evaluation parameter significantly. Hence the prepared Trihexyphenidyl microcapsules may prove to be potential candidate for safe and effective sustained drug delivery.

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