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FORMULATION AND *IN-VITRO* EVALUATION OF TOLBUTAMIDE MICROCAPSULES

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Abstract: Microcapsules were prepared by solvent evaporation method. Accurately weighted polymers (methylcellulose and ethyl cellulose) in different ratios were dissolved in 20ml of acetone to form a homogenous polymers solution. Core material, i.e., Tolbutamide was dispersed in it and mixed thoroughly. 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. In vitro dissolution profile of each formulation was determined by employing g USP XXII type 2 basket methods (900 ml of pH 6.8-phosphate buffer, 100 rpm, and 37±0.50C). Microcapsules equivalent to 100 mg of Tolbutamide was loaded into the basket of the dissolution apparatus.

Keywords: Tolbutamide, Microcapsules, Methylcellulose, Ethyl cellulose, Dissolution



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INTRODUCTION

Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules of many useful properties. In a relatively simple form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters. The definition has been expanded, and includes most foods. Every class of food ingredient has been encapsulated; flavours are the most common. The technique of microencapsulation depends on the physical and chemical properties of the material to be encapsulated. Many microcapsules however bear little resemblance to these simple spheres. The core may be a crystal, a jagged adsorbent particle, an emulsion, a Pickering emulsion, a suspension of solids, or a suspension of smaller microcapsules. The microcapsule even may have multiple walls [1]. **Fig-1** microcapsule shapes

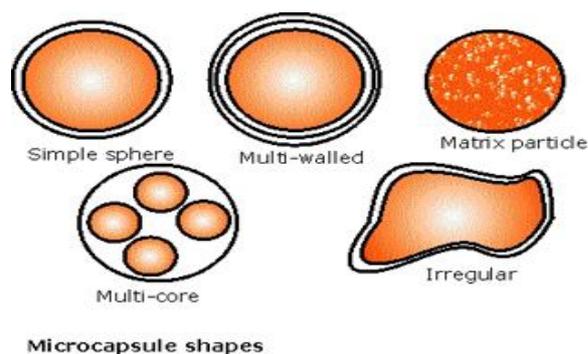


Fig-1 Microcapsule Shapes

MATERIALS AND METHODS:

Materials:

Tolbutamide was obtained as a gift sample from the Taj Pharmaceutical Pvt. Ltd. Mumbai. Polymers (methylcellulose and ethyl cellulose) were supplied as gift sample by star tech labs. India Ltd., Heavy liquid paraffin, petroleum ether was obtained from S.D. fine Chem. Ltd., Hyderabad (India), Span 80 and acetone was supplied from merk laboratories, all other chemicals and reagent used in this study were of analytical grade. **Fig-2.**the structure of tolbutamide

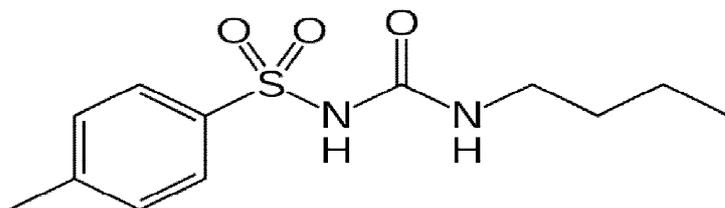


Fig-2. The Structure of Tolbutamide

Method:

Microcapsules were prepared by solvent evaporation method. Accurately weighted methylcellulose and ethyl cellulose in different ratios were dissolved in 20ml of acetone to form a homogenous polymers solution. Core material, i.e., Tolbutamide 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 [2,3]. 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 TOLBUTAMIDE MICROCAPSULES

INGREDIENTS	F1	F2	F3	F4
Methylcellulose 100 (mg)	50	50	50	50
Ethyl cellulose 100 (mg)	100	150	200	250
Tolbutamide (mg)	100	100	100	100
Acetone (ml)	20	20	20	20

Scanning Electron Microscopy:

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 (Indian Institute of Chemical Technology (IICT), Hyderabad, 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:

In vitro release studies: *In vitro* dissolution profile of each formulation was determined by employing g USP XXII type 2 basket methods (900 ml of pH 6.8-phosphate buffer, 100 rpm, $37\pm 0.5^{\circ}\text{C}$). Microcapsules equivalent to 100 mg of Tolbutamide 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 [4.7]. 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 DISCUSSION:

Preparative aspects of Polymer (methylcellulose and ethyl cellulose) 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 Tolbutamide 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 [5, 6]. 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 the Methylcellulose and ethylcellulose polymer, the quality of microcapsules formed was poor (**Figures 4 and 5**). 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 methylcellulose and ethyl cellulose polymer, 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 Tolbutamide and is 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. Petroleum ether or n-hexane was used to clean the micro particles since it removes liquid paraffin without affecting the integrity of the micro particles [8, 9].

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 [10]. After stirring the solution was filtered through Whatman filter paper and from the filtrate appropriate dilutions were made and absorbance was measured at 254 nm by using UV- spectrophotometer 1800 (Shimadzu).

TABLE 2: PERCENTAGE YIELD AND INCORPORATION EFFICIENCY OF TOLBUTAMIDE 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 [11, 12].

TABLE 3: MICROMERITIC PROPERTIES OF TOLBUTAMIDE MICROCAPSULES

Formulation code	Particle size (µm)	Angle of repose
F1	368.32± 1.01	17°55" ± 1.83
F2	362.58± 1.14	18°35" ± 3.85
F3	395.57± 2.5	21°40" ± 2.75
F4	435.84± 1.5	23°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. 3-6**). 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 [13].

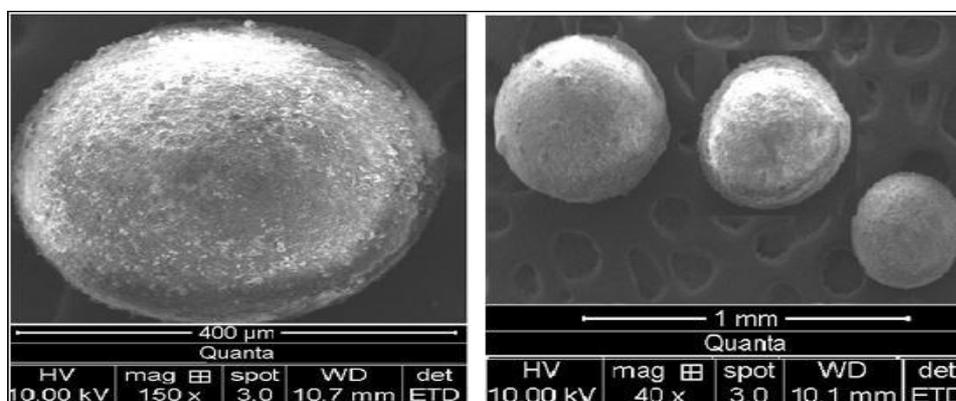


FIG. 3: SCANNING ELECTRON MICROSCOPY (SEM)

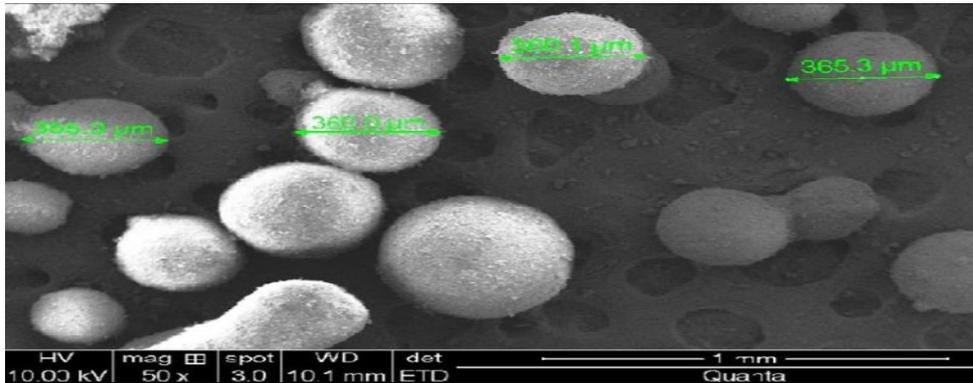


FIG. 4: SCANNING ELECTRON MICROSCOPY OF FORMULATION F2

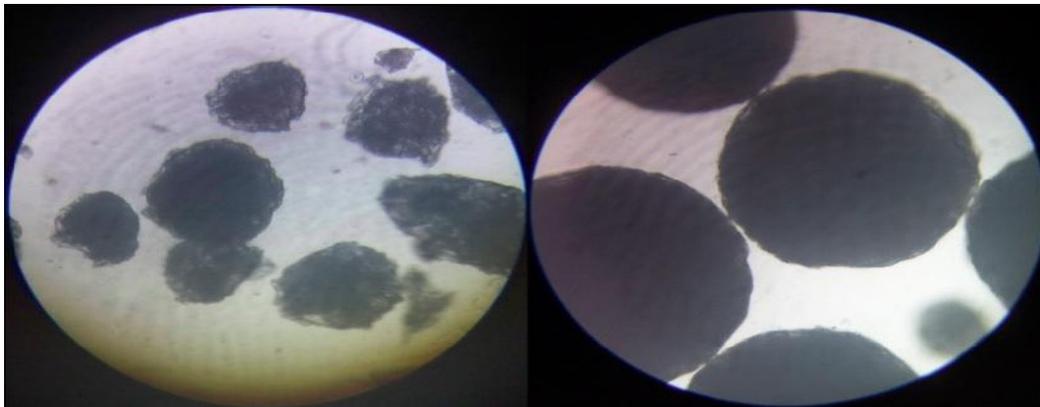


FIG. 5: MICROSCOPIC EVALUATION OF PREPARED MICROCAPSULES
F1 & F2 RESPECTIVELY

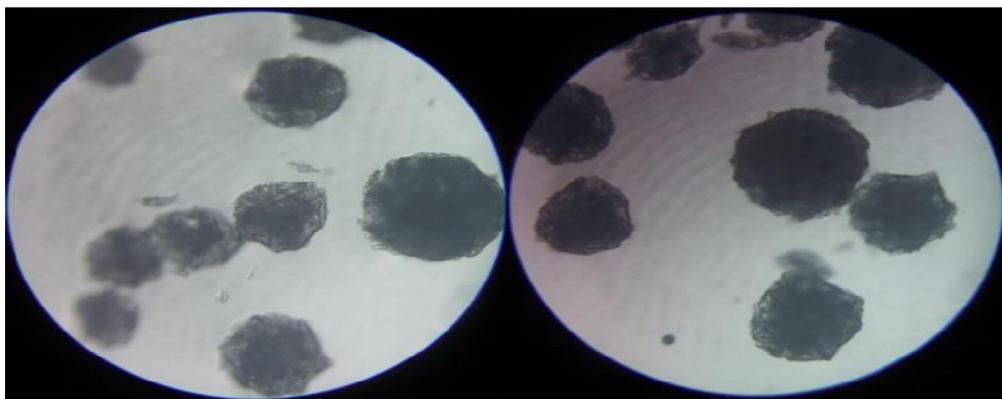


FIG. 6: MICROSCOPIC EVALUATION OF PREPARED MICROCAPSULES
F3 & F4 RESPECTIVELY

Drug release:

In vitro release studies were carried out using USP XXII type 2 basket assemblies. The release profile obtained for all the four formulations. It is important to note that the dissolution behaviour of granules and powders is greatly influenced by their wet ability, surface area, and particle size distribution. 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 [14]. 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 [15].

CONCLUSION:

The solvent-evaporation method using polymers (methylcellulose and ethyl cellulose) at optimum levels was effective for the formation of Tolbutamide 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 Tolbutamide microcapsules may prove to be potential candidate for safe and effective sustained drug delivery.

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