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Review Article

A Review on Orodispersible Tablets Prepared Using Spray Dried Sustained Release Microparticles

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Abstract:

Advancements in Novel Drug Delivery Systems (NDDS) has the objective for designing of dosage forms, which are convenient to be manufactured and administered, devoid ofside effects, giving desiredrelease and increased bioavailability to achieve better patient compliance.Though solid oral drug delivery systems,preferably, tablets are the most widely accepted dosage forms, having compactness, uniform dose and non-invasive drug delivery. Inspite of these advantages, dysphasia is themost common disadvantage of conventional dosage forms. This seems to affect about 35% of the general population and related with a number ofdisease conditions like Parkinsonism, motion sickness,mental disability, unconsciousness, unavailability of water etc. To overcome such problems, certaininnovative drug delivery systems, like 'Mouth Dissolving Tablets' (MDT) having Sustained Release property have been developed.Microparticles find the best way to attain such release. Solvent evaporation,Spray drying and extraction based processes are required for the preparations of microparticles.These are novel dosage forms which dissolve in saliva within a few seconds, when put on tongue.These dosage forms release the drug over a longer period of time overcoming the problem of frequent dosing in conventional dosage forms. The intent of this review article is to highlight the potential of microparticles in formulating the mouth dissolving tablets.

Keywords: Mouth dissolving tablets,sustained release microparticles, spray drying.

INTRODUCTION[1,2]

Despite tremendous advancements in drug delivery, the oralroute remains the perfect route for the administration of therapeuticagents due to low cost of therapy, ease of administration,accurate dosing, self-medication, avoidance, versatility, leadingto high levels of patient compliance. Tablets and capsules are themost popular dosage forms.But one important disadvantage of suchdosage forms is 'Dysphagia' or difficulty in swallowing. This seemsto affect nearly 35% of the population. This disability is alsoassociated with a number of disease conditions like:

1. Parkinsonism
2. Motion sickness

3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water.

Orally Disintegrating Tablet (ODT):

The Center of Drug Evaluation and Research (CDER) Nomenclature Standards Committee (in 1998) defined an orally disintegrating tablet (ODT) as ‘‘a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue’’ (Food and Drug Administration). The European Pharmacopoeia defined orodispersible tablets as ‘‘uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed’’ (Council of Europe 2002). It is worth mentioning that to date, the United States Pharmacopoeia does not have a published definition for ODTs.

Simply,it is a dosage form that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 sec. to 3 min. Most of the ODTs include certain super disintegrants and taste masking agents.

Ideal Properties of ODT[2,3]

A Mouth Dissolving Tablet should

a. Not require water or other liquid to swallow.

b. Easily disintegrate in saliva within a few seconds.

c. Have a pleasing taste.

d. Leave negligible or no residue in the mouth when
administered.

e. Be portable and easy to transport.

f. Be able to be manufactured in a simple conventional manner
within low cost.

g. Be less sensitive to environmental conditions like
temperature, humidity etc.

Advantages of ODT[2,3]

- Needless of water to swallow the tablet.
- Can be easily administered to pediatric, elderly and mentallydisabled patients.
- Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
    - Suitable for sustained/controlled release actives.
    - Allows high drug loading.
- Accurate dosing as compared to liquids.
- Dissolution and absorption of drug is fast, offering rapid onsetof action.
- Bioavailability of drugs is increased as some drugs are
- absorbed from mouth, pharynx and oesophagus through saliva
- passing down into the stomach
- Advantageous over liquid medication in terms ofadministration as well astransportation
- First pass metabolism is reduced, thus offering improvedbioavailability and thus reduced dose and side effects.

Limitations of ODT[2,3]

- Careful handling is required since the tablets usually have insufficient mechanical strength.
- The tablets may leave unpleasant taste or grittiness in mouth unless formulated properly.
- Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- Requires special packaging for properly stabilization & safety of stable product.

Mechanism of action of Superisintegrants[4]

The tablet breaks to primary particles by one or more of the mechanisms listed below:-

a. By capillary action
b. By swelling
c. Because of heat of wetting
d. Due to release of gases
e. By enzymatic action
f. Due to disintegrating particle/particle repulsive forces
g. Due to deformation

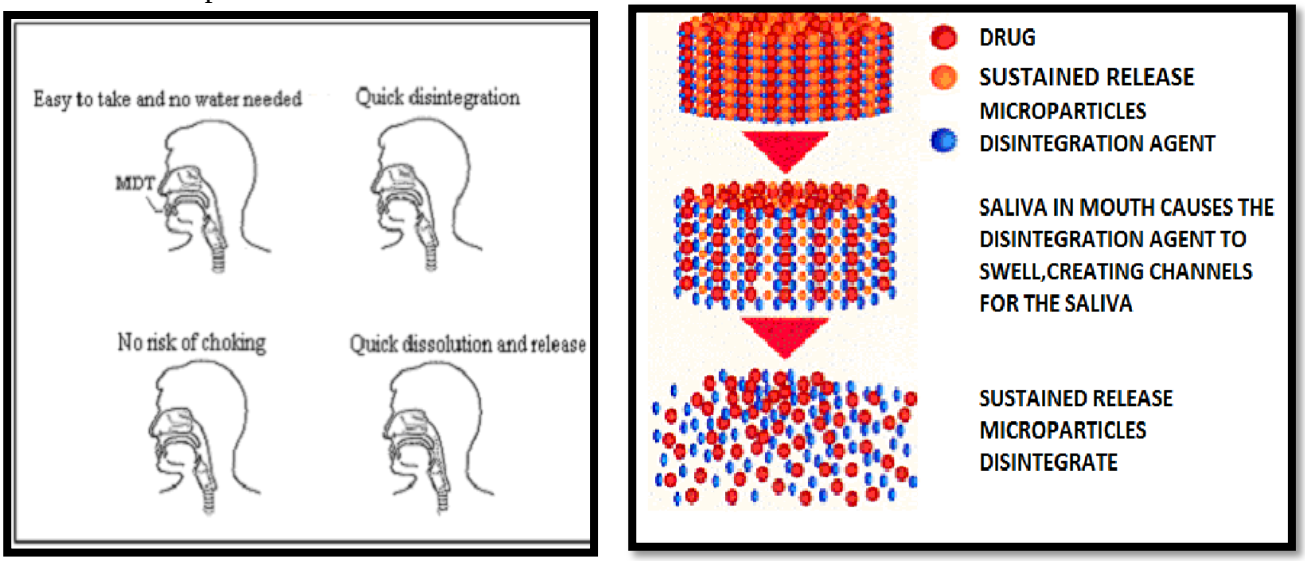

Fig.II:Disintegration of SR-ODT

Despite successes of ODTformulations, there are currently no formulations that can deliver an API(active pharmaceutical ingredient) in a sustained manner, e.g., delivery for 12 hrs. ODT formulations with sustained release properties would bring new benefits that were not possible before. One of the controlled release mechanisms is microparticulate controlled drug delivery.

TECHNIQUES USED IN THE PREPARATION OF MOUTH DISSOLVING TABLETS[4]

Some of the new advanced technologies which are commonly being used in last few decades aresummarized as:-

- Freeze drying/Lyophilization
- Molding
- Direct Compression
- Cotton Candy Process

- Spray Drying
- Sublimation
- Mass Extrusion

For the preparation of sustained release dosage form, one should be aware of the terms of controlled drug delivery.

Sustained release of drug: There has been a remarkable increase in the interest in sustained release dosage form, due to prohibitive cost of developing new drug entities, discovery of the new polymers and improvement in efficiency and safety provided by these. SRDDS is a modified dosage form that prolongs the therapeutic activity of the drug. Accordingly, a prodrug or analogue modification of the drug sustains blood level is considered as sustained release system. Several terms have been used to describe the various types of drug delivery systems intended to provide long duration of action.[5,6]

They are as follows:

- **Repeat action:** A dose of the drug is initially is released immediately after administration, which is usually equivalent to a single dose of conventional drug product. After a certain period a second single dose is released.
- **Sustained release:** This is a specific type of modified release dosage form that allows at least a two-fold reduction in the dosage frequency compared to conventional drug delivery system.
- **Controlled release:** The dosage form in which the drug is released in a planned, predictable and slower than conventional dosage form.
- **Delayed release dosage form:** This is a specific type of modified release dosage form that releases the drug at a particular time. E.g. Enteric coated tablet.

Advantages:

1. Minimizedlocal and systemic side effects.
2. Better drug utilization.
3. Decrease in total dose of the drug.
4. Prevents fluctuation of plasma drug concentration.
5. Better Bio-availability of the drug.
6. Improved efficiency in treatment.
7. Improved patient compliance.
8. Economy.

Disadvantages:

1. Dose dumping.
2. Reduced potential for accurate dose adjustment.
3. Need for additional patient education.
4. Slow absorption may delay the onset of activity, but this is probably unimportant during multiple regimes.

INTRODUCTION TO MICROPARTICLES AS DRUG DELIVERY SYSTEMS[7]

Micro-particles are the polymeric entities in the range of 1-1000μm.They cover two types of forms as Microcapsules which are micrometric reservoir systems and Microspheres which are micrometric matrix systems. **Microspheres** are essentially spherical in shape, whereas **microcapsules** may be spherical or non-spherical. Microparticles offer a method to deliver macromolecules by a variety of routes and effectively control the release of

such drugs. They may also be used in the delivery of vaccines and molecules such as DNA for use in gene therapy. Microparticles offer effective protection of encapsulated agent against degradation (e.g. enzymatic), the possibility of controlled and local delivery of the drug over periods ranging from few hours to months, and easy administration. The optimum effect of many medical treatments is obtained by maintaining the drug concentration in the therapeutic range over a sustained period of time. This is especially true for highly potent drugs, such as anti-cancer drugs. Administration of the entire drug dose at once using conventionalpharmaceutical dosage (e.g. tablets, bolus injection), the whole amount is rapidly released into the stomach, absorbed into the blood stream and distributed throughout the humanbody

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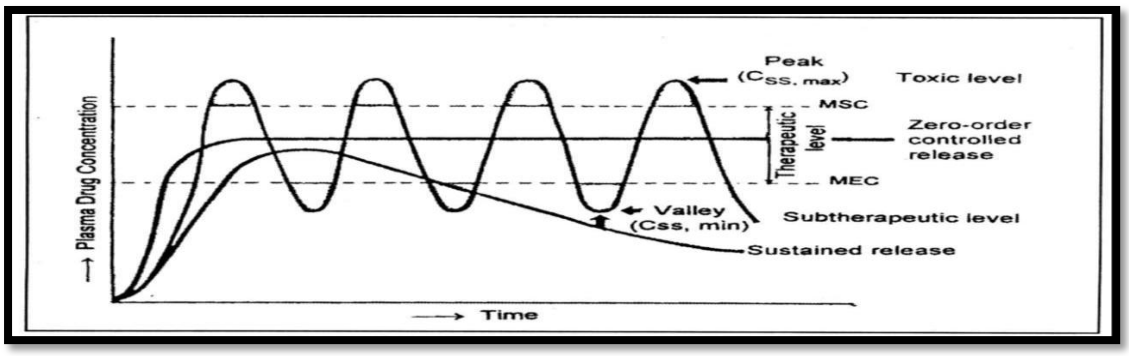

Fig.III:Concentration(c) vs. Time (t) profiles for conventional and controlled release drug delivery

As a result, the rate at which the drug its site of action is often high. Depending on the therapeutic range and administered dose, the risk of toxic side effects can be considerable. As no continuous drug supply is provided and as the human body eliminates the active agent, the concentration decreases again. This results in a fluctuating concentration of the drug levels in the plasma and the therapeutic range is attained during only very short time period.

TECHNIQUES FOR THE PREPARATION OF MICROPARTICLES:

- Solvent evaporation and extraction based processes:
  - Single emulsion process
  - Double emulsion process

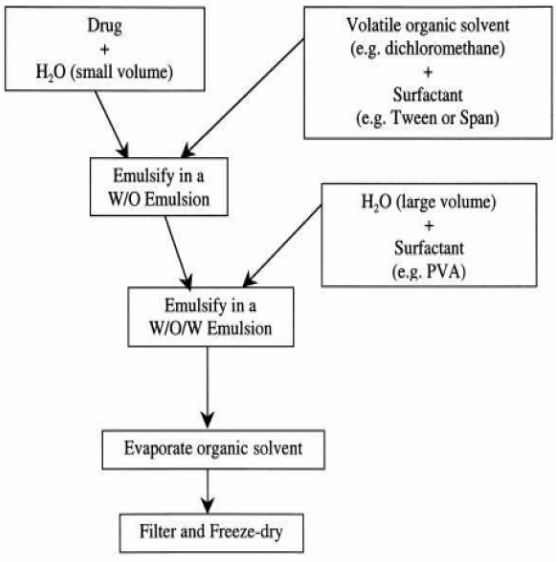

Fig.IV:Schematic of w/o/w in-liquid drying process for microparticle preparation

- Phase separation coacervation
- Spray drying
- Solvent extraction
- Chemical and thermal cross-linking
- Cross linking using a freeze-thaw technique

Of all the processes mentioned above,spray drying seems to have the capability to produce the microparticles which have the desired properties better than that produced by the other processes.

SPRAY DRYING [8]

Spray drying is one of the few crucial processes that can be used for the preparation of the microparticles ranging from 10-1000 µm. It is the continuous transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. The feed may be solution, slurry, emulsion, gel or paste, provided it is pumpable and capable of being atomized. It involves bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of liquid droplets. The hot air supplies the heat for evaporation and conveys the dried product to the collector; the air is then exhausted with the moisture.

Three types of atomizers are commercially used.They are;

- Rotary atomizer
- Pressure nozzle
- Two-fluid nozzle.

The feed droplets while losing its moisture to hot air remain at temperatures much below the hot air temperature for a very short time. Hence spray drying is essentially known as "Low Temperature Drying". The dried product can be in the form of powders, granules, or agglomerates depending upon the physical and chemical properties of the feed, the dryer design and final powder properties desired.

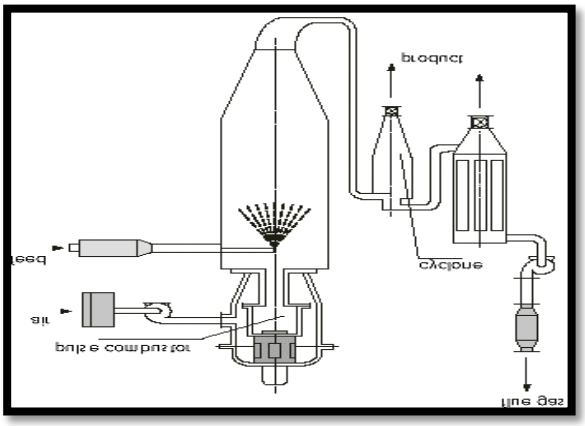

Fig:V-Laboratory Spray Dryer

Principle

There are three fundamental steps involved in spray drying.

1) Atomization of a liquid feed into fine droplets.

2) Mixing of these spray droplets with a heated gas stream, allowing the liquid to evaporate and leave dried solids.

3)Dried powder is separated from the gas stream and collected.

Controlling parameters :

The pharmaceutical spray-dried products have important properties like

-Uniform Particle size,

-Nearly spherical regular particle shape,

-Excellent Flowability,

-Improved Compressibility,

-Low Bulk Density,

-Better Solubility,

-Reduced Moisture Content,

-Increased Thermal stability, and suitability for further applications.

Advantages of spray drying:

Able to operate in applications that range from aseptic pharmaceutical processing to ceramic powder production.

- ✓ It can be designed to virtually any capacity required. (Feed rates range from a few pounds per hour to over 100 tons per hour).
- ✓ The actual spray drying process is very rapid, with the major portion of evaporation taking place in less than a few seconds.
- ✓ Adaptable to fully automated control system that allows continuous monitoring and recording of very large number of process variables simultaneously.
- ✓ Wide ranges of spray dryer designs are available to meet various product specifications.
- ✓ It has few moving parts and careful selection of various components can result in a system having no moving parts in direct contact with the product, thereby reducing corrosion problems.
- ✓ It can be used with both heat-resistant and heat sensitive products.
- ✓ As long as they are can be pumped, the feedstock can be in solution, slurry, paste, gel, suspension or melt form.
- ✓ Offers high precision control over Particle size, Bulk density, Degree of crystallinity, organic volatile impurities and residual solvents.
- ✓ Powder quality remains constant during the entire run of the dryer. Nearly spherical particles can be produced, uniform in size and frequently hollow, thus reducing the bulk density of the product.

Disadvantages of spray drying

- ➢ The equipment is very bulky and with the ancillary equipment is expensive.
- ➢ The overall thermal efficiency is low, as the large volumes of heated air pass through the chamber without contacting a particle, thus not contributing directly to the drying.

Applications

Many pharmaceutical and biochemical products are spray dried, including antibiotics, enzymes, vitamins, yeasts, vaccines, and plasma.

There are various application of spray drying like Microparticles formulation, Granulation and tabletting, Aerosol formulation, Coating applications, Dry emulsions and dry elixirs formulation.We have mainly discussed on Microparticles ODT formulation.

Microparticle Formulation

There are mainly two forms of microparticles that are produced by spray drying technique.

- ➢ Microspheres
- ➢ Microcapsules

Following are flow charts showing formulation of them:

Microspheres:DRUG + POLYMER(S)

⇩

DISSOLVE IN A COMMON SOLVENT (OR COMBINATION OF SOLVENTS) TO FORM A SOLUTION.

⇩

SPRAY DRYING

⇩

MICROSPHERES.

Microcapsules:

POLYMER+DRUG

⇩

DISSOLVE IN A SOLVENT (OR COMBINATION OF SOLVENTS) IN WHICH DRUG IS NOT SOLUBLE.

⇩

FORMATION OF SUSPENSION/EMULSION

⇩

SPRAY DRYING

⇩

MICROCAPSULES.

❖ General requirements for the drugs and polymers to be spray dried:

- The solvent should be selected on the basis of solubility of drug substance in it and boiling point of the solvent.
- The melting point of the drug substance should be more than the inlet temperature so as to avoid the degradation of the same.
- The selection of ratio of drug to polymer should be done on the trial and error basis.The polymer concentration should generally be more so as to give better coating,taste masking and entrapment.
- Another criteria includes the addition of surfactant(eg:Tween-80) to improve the particle smoothness and entrapment efficiency.

EVALUATION OF MICROSPHERES[9,10,15,16]

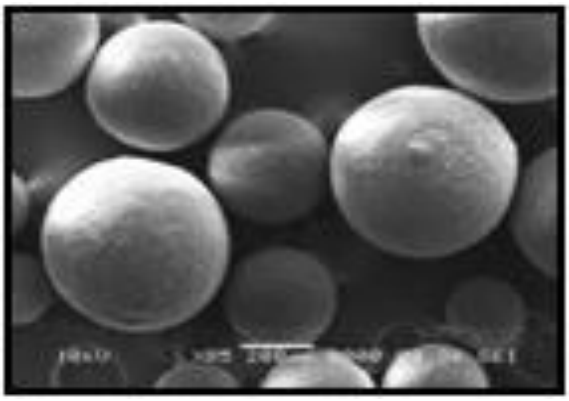

Fig-VI:Microscopic view of microspheres.

1. Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning

electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microspheres.

2. Electron spectroscopy for chemical analysis:

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surfacial degradation of the biodegradable microspheres.

3. Attenuated total reflectance Fourier Transfom- Infrared Spectroscopy:

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

4. Density determination:

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressureat different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

5. Isoelectric point:

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different Ph values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

6. Angle of contact:

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing

and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres.

7. *In vitro* methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating *in vivo* conditions has led to development of anumber of *in vitro* release methods for buccal formulations; however no standard *in vitro* method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed. The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements, paddle25, 26, 27 and basket 28, 29. Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.

***In vivo* methods**

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrants at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However the most widely used methods include *in vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

9. Swelling Index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula Swelling index= (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 100.4

Entrapment efficiency

The capture efficiency of the microspheres or the percent entrapment can be

determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:

% Entrapment = Actual drug content/Theoretical drug content x 100

Stability studies

By placing the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition
2. Room temperature (27+/-2^{0}C)
3. Oven temperature (40+/-2 ^{0}C)
4. Refrigerator (5 ^{0}C -8^{0}C).

It was carried out of a 60 days and the drug content of the microspheres was analysed.

- The prepared microspheres are also evaluated for thermal analysis like:
  - Differential Scanning Calorimetry(DSC)
  - Thermogravimetric Analysis(TGA)
- Other important parameters include:
  - Bulk density(D_b):

$D_b=M/V_b$

;Where, M is the mass of powder

$V_b$is the bulk volume of the powder.

  - Tapped density(D_t):

$D_t = M / V_t$;Where, M is the mass of powder

$V_t$is the tapped volume of the powder.

  - Carr's compressibility index
  - Hausner's ratio
  - Angle of repose

Table -I:Relationship between % compressibility and flow ability[3]

Sr. No.	% Compressibility	Flow ability
1	5 – 12	Excellent
2	12 – 16	Good
3	18 – 21	Fair Passable
4	23 – 35	Poor
5	33 – 38	Very Poor
6	< 40	Very Very Poor

Table -II: Angle of Repose as an Indication of Powder Flow Properties[3]

Sr. No.	Angle of Repose	Type of Flow
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

Preparation of orodispersible tablets of microspheres:

Microspheres formula that gives the best in vitro release results is selected for preparation of ODTs by direct compression technique. The microspheres can be formulated into the ODTs using different types of superdisintegrants.Generally used superdisintegrants are:

- Crospovodone(Cross linked povidone)
- Croscarmellose sodium
- Sodium Starch Glycolate[20]

Other added excipients include:

- Flavours(eg.mango,strawberry)
- Sweeteners(eg.sodiumsachharine,Aspartame)

EVALUATION OF PREPARED SR-ODT FORMULATIONS [3]

- **Thickness:** Tablet thickness can be measured using a simple procedure. 5 tablets are taken and their thickness is measured using Varniercalipers.
- **Weight variation[19]:**20 tablets are selected randomly from the lot and weighed individually to check for weight variation. Weight variation specification as per I.P. is shown in following table:

Table-III: Weight Variation Specifications

Sr. No.	Average weight of Tablet	% Deviation
1	80 mg or less	±10
2	More than 80 mg but lessthan 250 mg	±7.5
3	250 mg or more	±5

- **Hardness:** Hardness or tablet crushing strength (kg) is the force required to break a tablet in a diametric compression and is measured using Monsanto tablet hardness tester(eg. Monsanto).It is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. Hardness is expressed in kg/cm2.

- **Friability:**Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula

$$F = \frac{W(\text{initial}) - W(\text{final})}{W(\text{initial})} \times 100$$

- **Wetting time:**Wetting time is closely related to the inner structure of the tablets and to thehydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders. Wettingtime corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter.Ten millimeters of water-containing Eosin, a watersoluble dye, is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

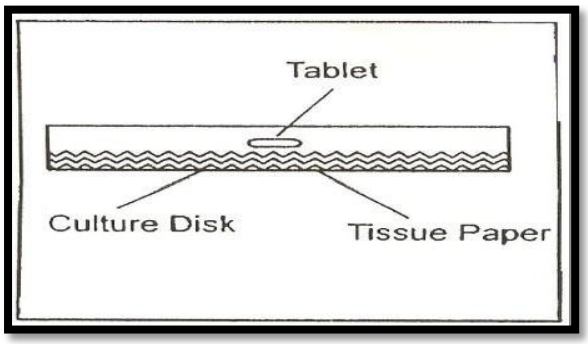

Fig.VII: Schematic representation of wetting time

- ***In-Vitro* drug release*:*** Release of the drug *in vitro*, is determined by estimating the dissolution profile.

Dissolution test: USP 2 Paddle apparatus is used and paddle is allowed to rotate at 100 rpm .0.1 N HCl is used as a pH 1.2 solution for first two hours and phosphate buffer (PH 6.8) (900 ml) is used as a dissolution medium for remaining time to study the sustained release of the drug.

- **Mechanical Strength*:*** Tablets should possess adequate strength to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters to evaluate a tablet for its mechanical strength.

CONCLUSION:

The oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance.The microparticles offers a variety of opportunities such as protection and masking, better processability, improved bioavailability, decreasing dosing frequency, improve stability, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. From the above review it can be concluded that spray drying can be effectively used as a tool for the preparation of sustained release microparticles to formulate them into orodispersible tablets. These tablets will bring a new scope for the development of dosage forms which will benefit the elder patients who cannot swallow even the sustained release medications.

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