IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

SPANSULES A NEW METHOD OF DRUG DELIVERY

Vivek V. Bawane[1] , Prof. M.B. Wankhade[2], Prof. Swati P. Deshmukhr[3], Dinesh M. Deokar[4] , Divyani S. Tiwaskar[5] .

[1]Student Shraddha Institute Of Pharmacy Washim.

[2]Lecturer Shraddha Institute Of Pharmacy Washim.

[3]Student Shraddha Institute Of Pharmacy Washim.

[4]Student Shraddha Institute Of Pharmacy Washim.

[5]Student Shraddha Institute Of Pharmacy Washim.

Abstract

Spansules are the tablets form which are modest and advanced medicine delivery system. Multiple medicine can be delivered by the spansules capsule. Spansules are made up of hard gelatine capsules and its contains active cures in the form of grains or micro-pellets. The external gelatine shell give stability to grains and release medicine at the needed time. Spansules are dissolves sluggishly(having slow dissolving rates) and follows up the zero order kinetics and also furnishing tube medicine attention constantly followed by controlled release of medicine.

Keywords :- spansules, grains, medicine , systems , components or granules.

INTRODUCTION

Spansules are a type of advanced medicine delivery system that involve packing an active component inside a capsule shell in the form of grains or micro patches of varying sizes. This type of capsule protects the grains or active component from its girding terrain and releases the drug at a needed time.[1]Spansules relate to a medicine delivery system that facilitates the gradational release of drug over an extended duration. Spansules correspond of atomic globules or bullets that are enveloped in a distinct polymer coating. Spansules are constantly employed to manage habitual medical conditions like hypertension, diabetes, and psychiatric diseases.[2] Spansules are designed to gradationally release drug, performing in a harmonious remedial attention of the medicine in the body. This controlled release medium can enhance treatment efficacity and minimize

the liability of adverse responses. Spansules are offered in different phrasings similar as capsules, tablets, and bullets. tradition specifics are generally recommended by a healthcare professional and must be consumed precisely as instructed to achieve the stylish possible treatment results.[3] Spansules are designed to release one or further medicines over a specified period of time. They're generally made up of grains or bullets that contain one or further active medicinal constituents(APIs), and are carpeted with a slow- dissolving polymer that controls the release of the drug. The coating of the Spansules determines the release pattern of the medicine, and can be designed to release the drug at different and predetermined times.[4] utmost of all polymeric coating ways have been extensively applied in pharmaceutical assiduity for numerous reasons similar as taste masking, defensive hedge, stability enhancement, and substantially controlled release of medicines for the medication of colorful lozenge forms.[5] bullet lozenge forms and their expression design have shown numerous advantages and inflexibility in enhancing Remedial safety and energy. As a result, on numerous occasions, inventors prefer to elect bullet lozenge forms as the main choice during lozenge form development.[6] This are substantially transparent in appearance we can see Fluently colour grains in it. This system can produce a rapid-fire increase in tube attention Of medicines similar as analgesic ,anti-inflammatory, anti-hypertensive, etc. That are requested Instantly exercise the remedial effect followed by a prolonged release phase to avoid Repeated administration. [7]The dissolution rate of fleece depends upon the solubility and

Consistence of coating(1- 200 microns).[8] The consistence of coating allows the sluggishly dissolving Of a cure over a long period of time. A spansules contains hundreds of coloured bullets or grains divided into 3 to 4 groups which differ in their consistence of time- detention coating. These bullets or grains give lading cure and release medicines at 2 or 3 hours, 4 or 6 hours, and 6 or 9 hours. The medicine release depends on saturation of humidity to the carpeted patches(core) performing in the lump, ruptures the Coating, therefore followed by releasing medicine.[9]

Definition:

Spansules are defined as capsules containing drugs(in form of grains), carpeted With accoutrements having slow dissolving rates so that the cure is delivered at different Specific time. In other words, it’s combination of two words i.e. span and capsule, hence it’s a capsule that sluggishly gives off drug over a different span of time.

Fig 1 Spansules

Advantages of Spansules: -

• Spansules are the lozenge form that provides controlled as well as sustained release for single or multiple medicine

• rules.

• Reduce side goods by perfecting patient compliance.

• Controls medicine attention in systemic rotation performing in enhanced bioavailability.

• Enhances medicine declination in GIT

• Taste masking is one further salutary aspect

• Controlled and sustained release Spansules give controlled and sustained release of drug, which can help maintain a remedial position of the medicine in the body and reduce the need for repeated dosing.

• Advanced case compliance By reducing dosing frequence and furnishing a more accessible dosing schedule, Spansules can ameliorate patient compliance with their drug authority.

• Enhanced bioavailability The controlled release of drug from Spansules can enhance medicine declination in the gastrointestinal tract(GIT) and ameliorate bioavailability.[10]

Disadvantages of Spansules:

• Lack of in vitro- in vivo correlation

• occasionally cure jilting may do.

• The systemic vacuity is dropped as compared to immediate- release conventional capsules.

• Poor in vitro- in vivo correlation as compared to conventional one.

• The change in tube medicine situations may lead to rush of side goods especially[11]

• medicine with small remedial indicator(TI) when over drug do

• Complicated process and requires skill labour to prepare this type of phrasings.

• medicine with small remedial indicator(TI) when over drug do

• Complicated process and requires skill labour to prepare this type of phrasings.

• toxin caused due to long amusement medications is delicate to treat.[12]

Classification of oral CDDS:

1. Nonstop Release System
    a) Dissolution controlled release systems
    b) Prolixity controlled release systems

Dissolution and prolixity controlled release systems

    c) Ion exchange resin medicine complexes
    d) pH dependent phrasings
    e) Bibulous pressure controlled system
    f) Hydrodynamic pressure controlled systems
    g) Slow dissolving mariners and complexes

2. Delayed Conveyance and nonstop release system
    a) Altered viscosity system
    b) Mucoadhesive system
    c) Size- grounded system
3. Delayed Release System
    a) Intestinal release system
    b) Colonic release system

Medicine release from Spansules

The coating has been formulated to exhibit sensitivity towards alterations in pH levels or enzymatic activity within the gastrointestinal tract, thereby facilitating its dissolution or disintegration. Improper design of the coating can result in limitations such as dose dumping or incomplete drug release. It should be noted that Spansules not be universally applicable to all drug types or formulations. This is because certain drugs may necessitate immediate release or specific delivery systems, as stated in reference.[13]

Types of drug release

1. Sustained release
2. Controlled- release lozenge form
3. Extended release
4. Delayed release
5. reprise action medicine delivery system
6. Dragged release system
7. Time release medicine delivery system
8. point-specific and receptor release

Methods of Preparation of Granules for Spansules:

1. Coacervation- phase separation
2. Spray drying
3. Spray congealing
4. Pan coating
5. Solvent evaporation
6. Fluidized bed technology
    1) Coacervation- phase separation

Coacervation- phase separation is a process used in the expression of Microencapsulated medicine delivery systems. It involves three main way.Polymer selection and dissolution The first step involves opting a suitable polymer and Dissolving it in a detergent to form a polymer result. The polymer should have the capability to form a Coacervate phase when mixed with a suitable Coacervation agent. Coacervation The polymer result is also mixed with a coacervating agent, which is a Substance that induces phase separation of the polymer result into two phases a thick Polymer-rich coacervate phase and a dilute supernatant phase.[14]

2) Spray drying

Spray drying is a generally used system for coating medicine patches or grains. In

This system, the medicine is first dissolved or suspended in a coating material, which is also scattered as a fine mist into a heated chamber. As the driblets of the mist move through the chamber, the detergent evaporates, leaving behind a dry, coated flyspeck or scrap. The coating solidifies upon contact with the hot air, forming a thin film around the medicine.[15] Spray drying is a rapid-fire, single-stage process that can be used for thermolabile Substances that might be damaged by exposure to high temperatures for long ages of Time. It's also fairly easy to gauge up, making it a popular choice for largescale Manufacturing of carpeted medicine patches or gran.

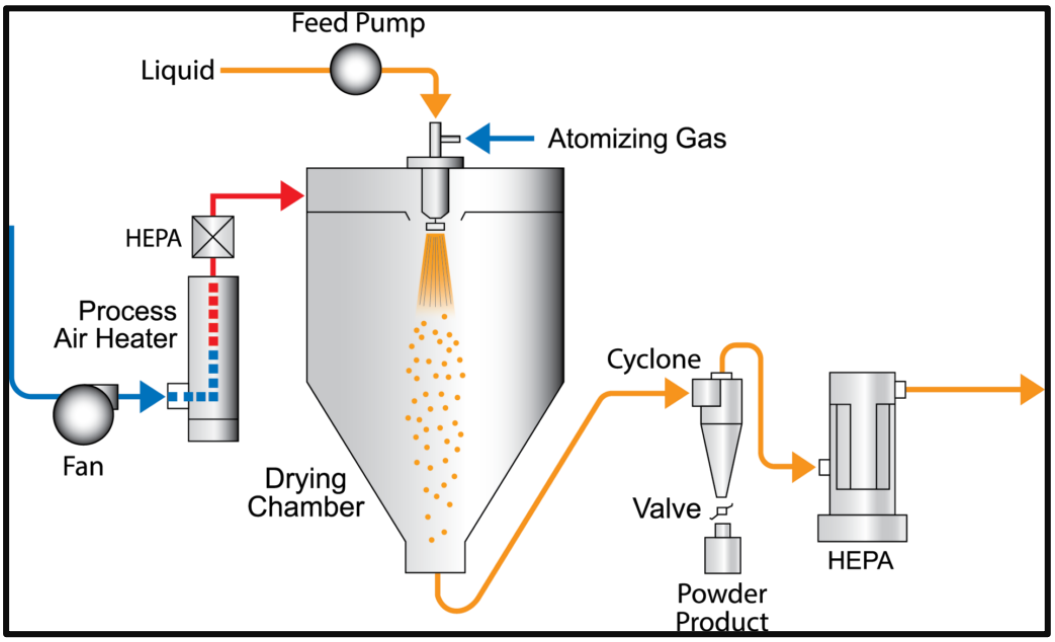

Fig 2 Spray drying

3) Spray congealing

In spray congealing, the substance being comminuted is melted at high temperature and

Also scattered through a snoot to form driblets which are also solidified by passingThrough a cool air sluice. The coating solidification takes place by thermally Congealing a molten coating material, not by evaporation of a detergent like in spray

Drying. This system is particularly useful for heat-sensitive substances that can not be

Exposed to high temperatures during the coating process.

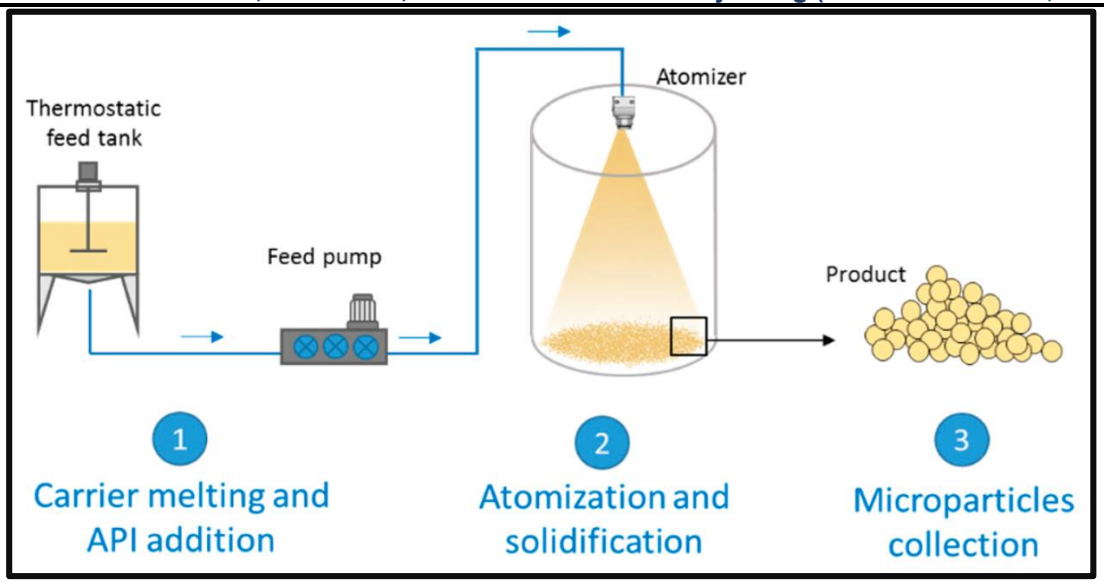

Fig 3 Spray congealing

4) Pan coating

Pan coating is a generally used system for sheeting small patches or bullets. The solid Patches with a size lesser than 600 microns are considered necessary for effective Coating. In this system, the patches are tumbled in a coating visage while the coating Material is sluggishly applied. The active component is generally carpeted onto colorful Globular-structured patches. The coating result is applied by grinding spray onto the Solid core material. To remove the coating detergent, a blast of warm air is passed ove

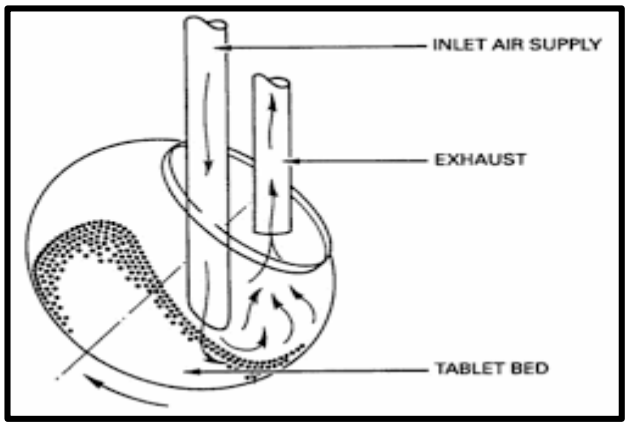

Fig 4 Pan coating

The coated accoutrements . This process is repeated several times until the asked coating consistence is achieved. Pan coating is a fairly simple and cost-effective system of coating patches and is extensively used in the pharmaceutical assiduity[16]

5) Solvent evaporation

Detergent evaporation is a common system used in the medication of microcapsules. In This process, the coating material is dissolved in a unpredictable detergent that's immiscible With the liquid vehicle phase. A core material is also dispersed in the coating result With shifting to gain invariant- sized patches. The grains size can be controlled by Varying the shifting rate, the attention of the coating material, and the type of Detergent used. A variety of film- forming polymers can be used as coating accoutrements in the solvent evaporation system. Exemplifications include polyvinylpyrrolidone, polyethylene, Polyvinyl alcohol, and polyacrylic acid. The choice of coating material depends on the asked parcels of the microcapsules, similar as stability, release rate, and comityWith the core material. Solvent evaporation is a protean and scalable system for the medication of carpeted grains and is extensively used in colorful fields, similar as Medicine delivery, food and libation, and particular care products.[17]

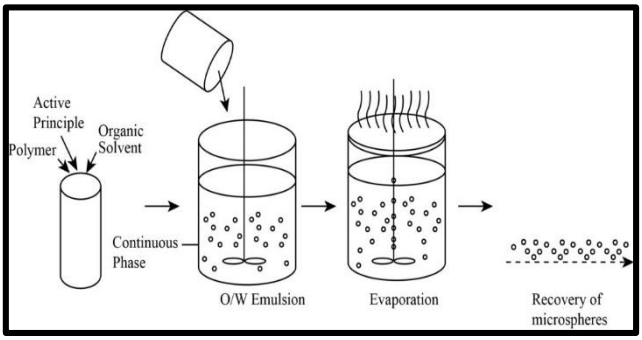

Fig 5 Solvent evaporation

6) Fluidized bed technology

Fluidized bed technology is a system used for coating patches with a liquid coating Material. In this process, the patches are suspended in a chamber containing a sluice Of air or gas that's fleetly flowing overhead. As the gas flows through the patches, it Causes them to come fluidized, carrying like a liquid, which creates a homogeneous Mixing of patches. Liquid coating material is also scattered onto the fluidized patches, Forming a invariant coating on the flyspeck shells. The rapid-fire evaporation of the liquid Coating material due to the high temperature and tailwind helps in the conformation of an External rigid subcaste on the patches with the needed consistence.

The fluidized bed technology can be used to cover colorful types of patches, including Maquillages, grains, and bullets, with different accoutrements , similar as polymers, waxes, Sugars, and other coating agents. The system offers several advantages, including Invariant coating consistence, high coating effectiveness, and controlled release of the active Constituents. [18]

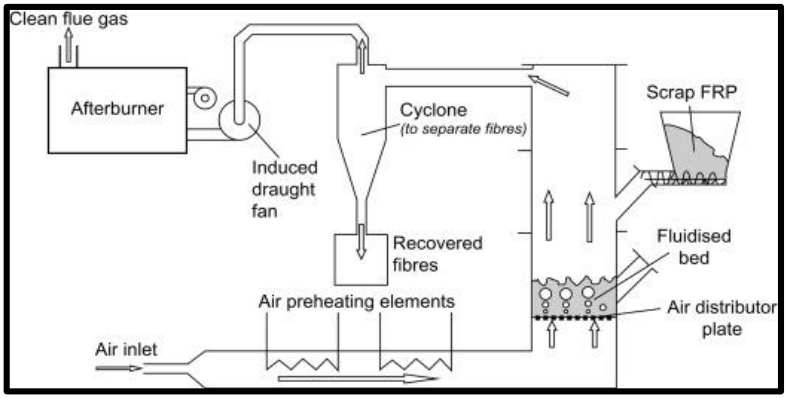

Fig 6 Fluidized bed technology

- **MOA of Spansules**

How Spansules acts every medicine flyspeck or scrap which is incorporated In Spansules associates with a material having slow dissolving exertion When these carpeted tablets are pressed into tablet form can be defined as SPACETABS or in form of capsules defined as SPANSUSLE. In Spansules, Medicine dissolution can be governed by microencapsulation. When the coating of The medicine grains gets dissolved medicine is released and now ready for dissolution. By changing the coating consistence, varying the composition, medicine release can Be destined. Spansules can not be masticated or broken because it may lead To damage of coating material.[19]A Spansules contains numerous grains which are different from each other on the Base of coating of consistence. These types of grains deliver a medicine at a Destined rate, first of all, the grains give lading cure followed by Medicine release at different time span. These coated grains deliver medicines at 2 – 3 Hours, 4- 6 hours, and 6- 9 hours. Medicine release is dependent on humidity Saturation into the coating of patches which causes lump of consistence Material followed by rhapsody performing in the medicine release([20]Spansules are the stylish illustration of dissolution release systems. Basically Hydrophobic or hydrophilic polymers are used in combination or in single. Some exemplifications are cellulose acetate phthalate, gelatin, and polyvinyl alcohol.[21]

- **Limitation of Spansules**

Spansules have some limitations, including The correlation between the in vitro release characteristics of Spansules and their in vivo performance isn't well- established due to limited available data. The use of Spansules entails a threat of cure jilting in the event of damage or

Concession. Cure jilting refers to the rapid-fire release of drug, which can Result in adverse goods. The Spansules lozenge form exhibits reduced systemic vacuity in comparison to Other forms of drug due to its gradational and prolonged release of the medicine over An extended period.[22]Cure jilting may be a reason for system failure. Systemic vacuity of the medicine is low. Complex to formulate, professed labor is needed. Precious.[23]Complex expression The expression of Spansules can be complex and requires Professed labor to produce, which can increase the cost. Advanced cost Spansules can be more precious than other lozenge forms due to the Complex expression process and technical outfit needed for product.[24]

- **Application of Spansules**

• Application of Spansules

• Spansules could be used as amulti-dosage authority because the grains have different Density of coating material.

• Spansules can release medicine at different and predestine time span.

• grains with the thinnest subcaste of coating material will release the original or lading Cure.

• Increases patient compliance by adding the effectiveness of cure.[25]

- **LITERATURE REVIEW :**

• Spansules are a lozenge form which was considered as one of the Advanced Drug Delivery System. Multidrug medications can be delivered fluently by spansules or grains in capsule Technology. This type of delivery system designed to release a medicine or a cure at two Or further different rates or in different span of time.[26]This type of Delivery system can give a constant tube medicine attention over a wide range of time, Which can ameliorate treatment issues and reduce the threat of side goods. In addition to Furnishing sustained release, Spansules can also be used to deliver multiple medicines in a single Lozenge form.[27]It's suggested that the spansules are one of the stylish medicine delivery, in this form of Pharmaceutical expression the multiple medicine contents are being microencapsulated and filled In a capsule shell leading to effective medicine delivery. It has a slow dissolving rates and follows Zero order kinetics so give constant tube medicine attention followed by controlled Release of medicine.[28]

• Spansules are considered one of the most profitable medicine delivery systems. Multi-drug Authority is the crucial benefit of Spansules(capsules having grains.) Spansules are constructed For the release of API(medicine) at different rates and times. The first immediate/ slow- release Pattern gives an original medicine release which is followed by medicine release at a constant rate for an Extended time. This will affect in constant medicines being available for a long time of period. This Boluses form is useful to overcome repeated medicine dosing.[29]Developing spansule lozenge form of nifedipine using extrusion and spheronization Fashion provides effective control of delivery of medicines over the period of 8h. Nifedipine Bullets carpeted with hydrophilic hydroxypropyl methylcellulose polymer, hydrophobic polymer (ethyl cellulose), and semipermeable polymer(cellulose acetate) to sufficient weight gain. Wanted rate of release achieved by of mix of polymers after optimization of variable.[30] The need for iron remedy an es when a diagno is of an iron- insufficiency anaemia has been Made. Although this type of anaemia is common to all relations and periods, it's in gestation that it is most frequently detected. Occasionally the symptoms are sufficiently apparent for laboratory Examinations to be made. Veritably frequently, still, an iron- insufficiency anaemia, is present, but Remains undressed because the symptomatology wasn't egregious enough to arouse dubitation . Iron anaemia may be due to an shy immersion of iron from.[31] purpose of this paper is to report compliances on the effect of a long amusement medication of Belladonna alkaloids on the rudimentary gastric acid stashing of cases with peptic ulcer and habitual Hypertrophic

gastritis. The medication used comported of a gelatin capsule containing Belladonna alkaloids in the form of several hundred veritably small especially carpeted bullets. By Means of variations in the consistence and composition of the bullet coatings, decomposition at Differing time intervals is permitted. This, in tum, permits a prolonged release of the active Constituents.[32]In a arbitrary double-eyelesscross-over trial of 45 cases, it was set up that Demazin Chronosules capsules compared with Eskornade spansules produced a better effect in 16 Cases, an equal effect in 20 cases, a poorer effect in 5 cases and that 4 cases showed No enhancement on either medicine. It was also shown that there was a 73 rate of effectiveness With Demazin Chronosules capsules in discrepancy with 57 with Eskornade spansules. It's Concluded that Demazin Chronosules capsules will be a useful adjunct in the treatment of Vasomotor rhinitis and seasonal hay fever.When using an objective system of assessing nasal patency by means of air- inflow studies, the Results didn't always agree with the clinical findings. Research is continuing in the stopgap of Producing a further.[33] This composition provides a brief overview of Spansules, a new medicine delivery system. Spansules Are designed to release drug in a controlled manner, furnishing a sustained and harmonious Remedial effect. This delivery system involves recapitulating the medicine in a special coating That dissolves sluggishly, allowing the drug to be released gradationally over time. Spansules are classified as an Advanced Drug Delivery System due to their capability to grease controlled and sustained release of drug over an Extended duration. Spansules can be employed for the delivery of multiple medicines in a single Lozenge form, while also furnishing sustained release.[34]

Evaluation parameters of spansules

1. Flyspeck size

The most common ways to determine the flyspeck size distribution are sieve analysis, Stationary ray light scattering analysis, dynamic light scattering, etc. Above citation, ways Determine flyspeck size. All mentions styles can measure flyspeck size ranging from 1µm to 3mm.The patches size of grains in Spansules can be fluently assay with the help of simple Sieve analysis

2. Assay by Ultra Violet Spectroscopy For UV analysis following way to be followed

Sample medication 100 mg of medicine in 100 ml volumetric beaker. Addition of suitable detergent. Sonification to run Addition of buffer result of pH1.2 and blend Transfer 5 ml result to 50 ml volumetric beaker and make the volume by means of buffer sol. Of pH1.2

3. Procedure

Check the absorbance at a specific wavelength with the filtered part of the test result in

Comparison with a standard Result using a1.2 pH buffer. Calculate chance chastity with the following formula

Chastity = factual quantum of asked material × 100/ total quantum of material

4. Frangibility test

Frangibility of Spansules can be calculated as chance weight loss after 100 revolutions of 10

Gm of spansules in friabilator

5. humidity content
6. Humidity content can be calculated under specific conditions with sample heating. The weight
7. Loss can be calculated with the following formula17.
8. Humidity content = w2- w1 × 100/ w2- w1
9. Where,
10. W1 = Weight of the vessel with lid
11. W2 = Weight of the vessel with lid and sample before drying
12. W3 = Weight of the vessel with lid and sample after drying
13. 6. Loss on drying
14. In this system, an empty gauntlet was counted and dehydrated for 30 twinkles. 1 gm of medicine
15. Sample is placed in this gauntlet and kept in a furnace for roughly one hour at 250- 300 °C.
16. After 1- hour gauntlet is kept in a desiccator for cooling. After cooling gauntlet is counted again
17. For weight loss19.
18. LOD can be calculated with the following formula
19. Loss = W1- W2 × 100/ W1
20. Where;
21. W1 = original weight of the sample
22. W2 = Final retained weight on sample vessel after 10 cycles
23. 7. In – vitro release study Dissolution studies
24. Dissolution studies are performed in calibrated dissolution outfit. The medicine release profile
25. Can be prognosticated through UV Spectrophotometer.[35]

Conclusion

Spansules are the lozenge form in which one or further active component is kept inside the capsule Shell in form of patches or grains. In Spansules thick coating help active pharmaceuticalingredient from their girdled terrain and medicine release take place at a destined

Rate. Spansules provides a new area to explore. Expression of Spansules professed professional, Advanced and technical outfit is needed. It can be concluded that Spansules are the

Tablets from easy to manufacture with implicit benefits over conventional lozenge form.

Reference

1) Maurya R, Sharma PK, Malviya R. A review on controlled drug release formulation: spansules. International Journal of Pharma Sciences and Research. 2014; 5(03): 78-81

2) Biswal B, Karna N. Bhavesh Bhavsar., Formulation and Evaluation of Repaglinide Buccal Tablet: Ex Vivo Bioadhesion Study And Ex Vivo Permeability Study. J App Pharm Sci. 2014;4(05):96–103.

3) Parashar AK. Synthesis and characterization of temozolomide loaded theranostic quantum dots for the treatment of brain glioma. J Med Pharm Allied Sci [Internet]. 2021;10(3):2778–82. Available from: http://dx.doi.org/10.22270/jmpas.v10i3.1073

4) Biswal B, Karna N. Bhavesh Bhavsar., Formulation and Evaluation of Repaglinide Buccal Tablet: Ex Vivo Bioadhesion Study And Ex Vivo Permeability Study. J App Pharm Sci. 2014;4(05):96–103.

5) Lee BJ, Ryu SG, Cui JH. Controlled release of dual drugloaded hydroxypropyl methylcellulose matrix tablet using drug-containing polymeric coatings. Int J Pharm 1999;188:71-80.

6) Roland B. Tableting of coated pellets. Eur J Pharm Biopharm 1997;43:1-8

7) Leon Lachman, Herbert A. Liberman, Joseph L. Kang, The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,Bombay, Sustained Release Dosage Forms, 418-419.

8) Kuentz M, Rothenhauser B, Rothlisberger D. Time domain 1H NMR as a new method to monitor softening of gelatine and HPMC capsule shells, Drug Development and Industrial Pharmacy. 2006; 32(10): 1165-73.

9) Leon Lachman, Herbert A. Liberman, Joseph L. Kang, The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,Bombay, Sustained Release Dosage Forms, 418-419.

10) Leon Lachman, Herbert A. Liberman, Joseph L. Kang, The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,Bombay, Sustained Release Dosage Forms, 418-419.

11) Kuentz M, Rothenhauser B, Rothlisberger D. Time domain 1H NMR as a new method to monitor softening of gelatine and HPMC capsule shells, Drug Development and Industrial Pharmacy. 2006; 32(10): 1165-73.

12) Biswal B, Karna N. Bhavesh Bhavsar., Formulation and Evaluation of Repaglinide Buccal Tablet: Ex Vivo Bioadhesion Study And Ex Vivo Permeability Study. J App Pharm Sci. 2014;4(05):96–103.

13) Das Nandita G, Das Sudip K. Controlled Release of Oral Dosage Forms, Formulation, Fill & Finish. www.pharmtech.com, 2003: 13.

14) Shalin AM, Gaikwad Pd, Bankar VH, Pawar SP. Sustained Release Drug Delivery System; A review. International Journal of Pharmaceutical Research and Development, 2011, 12(12):

15) Klinjapo R, Krasaekoopt W. Microencapsulation of color and flavor in confectionery products. In: Natural and Artificial Flavoring Agents and Food Dyes. Elsevier; 2018. P. 457–94.

16) The principal rules were published in the official gazette vide notification No. F.28-10/45-H(1) dated 21” December 1945 and last amended vide GSR 700€ dated 28-09-2001https://www.slideshare.net/vinay3121992/vinay-spansule

17) Zhang Y, Xu C, Gu ZQ. China. In: Bioequivalence Requirements in Various Global Jurisdictions. Cham: Springer International Publishing; 2017: 59–74.

18) Zhang Y, Xu C, Gu ZQ. China. In: Bioequivalence Requirements in Various Global Jurisdictions. Cham: Springer International Publishing; 2017: 59–74.

19) Zhang Y, Xu C, Gu ZQ. China. In: Bioequivalence Requirements in Various Global Jurisdictions. Cham: Springer International Publishing; 2017: 59–74.

20) Zhang Y, Xu C, Gu ZQ. China. In: Bioequivalence Requirements in Various Global Jurisdictions. Cham: Springer International Publishing; 2017: 59–74.

21) Zhang Y, Xu C, Gu ZQ. China. In: Bioequivalence Requirements in Various Global Jurisdictions. Cham: Springer International Publishing; 2017: 59–74.

22) Rahi N, Kumar K. Nanosponges: a new era of versatile drug delivery system. Universal Journal of Pharmaceutical Research. 2017; 2(3): 30-33.

23) KPreeta, Chugh, Lhamo Y. An Assessment of vitamin Supplements in the Indian Market: Indian Journal of Pharmaceutical Sciences. 2012.

24) HadiMohd Abdul, Raghavendra Rao NG. Novel Technologies in Formulations: An Overview. World Journal of Pharmaceutical Research. 2012; 1(3): 427.

25) Jeong K, Kang CS, Kim Y, Lee Y-D, Kwon IC, Kim S. Development of highly efficient nanocarrier-mediated delivery approaches for cancer therapy. Cancer Lett [Internet]. 2016;374(1):31–43. Available from: http://dx.doi.org/10.1016/j.canlet.2016.01.050

26) Rinky Maurya et al (2014)

27) Abhilasha Bhadoriya et al (2023)

28) Gurleen Kaur et al (2016)

29) Kapil Kumar et al (2022)

30) Periyasamy Killivalavan et al (2017)

31) HERBERT KRAMER et al (1962)

32) DONALD BERKOWITZ et al (1956)

33) T. G. HERON et al (1972)

34) Bhadoriya A. et al (2023)

35) The principal rules were published in the official gazette vide notification No. F.28-10/45-H(1) dated 21” December 1945 and last amended vide GSR 700€ dated 28-09-2001https://www.slideshare.net/vinay3121992/vinay-spansule.