

## A DISCUSSION ON QUALITY CONTROL OF SUPPOSITORIES

CHINMAYA KESHARI SAHOO<sup>\*1</sup>, M.SUDHAKAR<sup>2</sup>, D.VENKATA RAMANA<sup>3</sup>, KOKKULA SATYANARAYANA<sup>4</sup>

<sup>1</sup>Assistant Professor, Department of Pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Telangana-500014. <sup>2</sup>Professor and Principal, Department of Pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Telangana-500014. <sup>3</sup>Professor, Department of Pharmaceutical Technology, Netaji Institute of Pharmaceutical Sciences, Toopranpet, Yadadri Bhongir, Telangana-508252. <sup>4</sup>Professor, Department of Pharmacognosy, Princeton College of Pharmacy, Korremula, Ghatkesar, Telangana-500088. Email: sahooc.chinmaya83@gmail.com

Received - 22.04.2017; Reviewed and accepted - 10.05.2017

### ABSTRACT

Suppository quality control includes physical and chemical aspects of the product. The physical analysis includes visual examination (physical appearance), uniformity of weight, uniformity of texture, melting point, liquefaction time, melting and solidification time, and mechanical strength. Chemical testing includes analysis of the activity and dissolution testing. The uniformity of texture can be assessed by sectioning a suppository longitudinally and laterally, and ensuring that each section presents a smooth, uniform surface.

**Keywords:** Quality control, weight, melting point, liquefaction time

### INTRODUCTION

Rectal dosage forms like suppositories have several advantages over oral route. In cases of nausea and vomiting act taking medication orally may induce emesis so that drug is vomited before it absorbed. Irritation to the stomach and small intestine associated with certain drugs can be avoided. Hepatic first pass elimination of high clearance drug may be avoided partially. Its contact with the digestive fluid is avoided, thereby preventing acidic and enzymatic degradation of some drug. It is useful in pediatric, geriatric and unconscious patient especially having difficulty in swallowing oral medicine [1, 2]. Hence for the proper development of rectal dosage form quality control studies are needed. Quality control procedures listed in the US Pharmacopeia (USP30-NF25) for manufactured suppositories include identification, assay, and, in some cases, water content, residual solvent, dissolution, and content uniformity:

**Identification:** Identification tests are commonly used for the identification and confirmation

of official articles.

**Assay:** Assay and test procedures are used to determine compliance with the pharmacopeial standards of identity, strength, quality, and purity. Chromatographic methods are commonly used for detection and quantitation.

**Dissolution:** Dissolution testing is used to determine compliance with the dissolution requirements if present in the individual monographs. The test measures the rate and extent of a drug dissolving in a defined medium under defined conditions.

**Water:** As many Pharmacopeial articles either are hydrates or contain water in adsorbed form, the determination of water content may be important in demonstrating compliance with Pharmacopeial standards.

**Content uniformity:** Content uniformity is required in some monographs to ensure the consistency of dosage units. These dosage units should have drug substance content within a narrow range around the label claim. Weight variation and content uniformity testing involving groups and individual dosage units are used.

**Residual solvents:** For pharmacopeial purposes, these are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. They are not completely removed

during processing but should be removed to the extent that is possible and reasonable.

#### Physical analysis

##### Visual examination

Color and the surface characteristics [3] of the suppository are relatively easy to assess. It is important to check for the absence of fissuring, pitting, fat blooming, exudation, sedimentation, and the migration of the active ingredients. Suppositories can be observed as an intact unit and also by splitting them longitudinally.

##### Shape

It is advisable to check the shape of the suppository to see if it is consistent, irrespective of whether the suppository is ogive or torpedo shaped.

##### Surface condition

The following can be checked: brilliance, dullness, mottling, cracks, dark regions, axial cavities, bursts, air bubbles, holes, etc.

##### Color

The intensity, nature, and homogeneity of the color should be verified.

##### Odor

Verification of odor can prevent confusion when similar suppositories are being processed. A change in the odor may also be indicative of a degradation process.

#### Compatibility studies [4, 5]

##### Fourier Transform Infrared Spectroscopy (FTIR)

The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. In this method, individual samples, as well as the mixture of drug and excipients, were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into the disc by applying pressure of 5 tons for 5 mins in a hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400  $\text{cm}^{-1}$  in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures. Then the peaks of the optimized formulation were

compared with pure drug and excipients. If there was no interaction between the peaks of drug and excipients of optimized formulation then it was said to be compatible.

#### Differential Scanning Calorimetry (DSC)

The compatibility of the drug with the excipients used for formulation development was tested using differential scanning calorimetry. Physical mixtures of drug and individual excipients in the ratio of 1:1 were taken and examined in DSC. Individual samples, as well as a physical mixture of drug and excipients, were weighed to about 5mg in DSC pan. The sample pan was crimped for effective heat conduction and scanned in the temperature range of 50-300°C. The heating rate of 20°C min<sup>-1</sup> was used and the thermogram obtained was reviewed for evidence of any interactions. Then the thermograms were compared with pure samples versus optimized formulation.

#### Melting range (melting point, melting zone)

Melting range or melting zone [6] is the term often preferred by some rather than melting point. Many suppository bases and medicated suppositories are mixtures, and so do not have a precise melting point. A number of different techniques are used to study melting behavior, including the open capillary tube, the U-tube, and the drop point methods. The results produced using different methods do not always agree, so it is important to use a consistent method. In general, the melting point should be equal to or less than 37°C. A non-destructive method can be used because if the suppository is melted before a measurement is made, the suppository constituents may be transformed into a metastable state. The melting test consists of placing a suppository on the surface of water thermostatically controlled at 37°C and verifying the complete melting of the suppository in a few minutes. This is not so much a measurement as an evaluation.

#### Liquefaction time

Liquefaction [7, 8] testing provides information on the behavior of a suppository when subjected to a maximum temperature of 37°C. The test [9] commonly used is Krowczynski's method which measures the time required for a suppository to liquefy under pressures similar to those found in the rectum (approximately 30 g) in the presence of water at 37°C. In general, liquefaction should take no longer than about 30 minutes. For Krowczynski's method, the apparatus consists of a 16 mm diameter glass tube, 235 mm long with an approximately 6mm diameter reduction at the base. One end is blocked with a small rubber stopper to facilitate cleaning after use. A thermostat graduated in tenths of a centigrade is used. The tube and thermometer are held in place by means of a large rubber stopper with two holes in a 225mm long tube with a 50mm diameter, fitted with lateral tubes to allow the water at 37°C from a constant-temperature water bath to circulate.

#### Melting and solidification time

The higher the melting point, the later the drug effects appear. If too high, the drug effect does not appear. The solidification temperature [10] is defined as the highest temperature occurring during the solidification of a supercooled liquid. Various methods are available to measure it, including Shukoff's method, in which the liquid is shaken in an evacuated flask until turbid and the temperature noted at which a transitory rise in temperature occurs during cooling. The European Pharmacopoeia also describes a procedure that involves heating the material, then allowing it to cool slowly while stirring. The temperature is recorded at 1-minute intervals. The cooling curve normally passes through a minimum, which indicates a supercooled melt. Heat is liberated during crystallization and the temperature-time curve rises. The maximum temperature in this phase is the solidification temperature.

#### Mechanical strength/crushing test

Suppositories can be classified as brittle or elastic by evaluating the mechanical force [11] required breaking them. Tests have used that measure the mass (in kilograms) that a suppository can bear without breaking. A good result is at least 1.8–2 kg pressure.

The suppository is positioned in an upright position and increasing weights are placed on it until it loses its structure and collapses. The purpose of the test [12] is to verify that the suppository can be transported under normal conditions, and administered to the patient.

#### Weight variation test

20 suppositories [13, 14] were weighed and average weight was found out. After that, each suppository was weighed individually on an electronic balance. Not more than 2 individual suppositories deviate from average weight by more than 5% and no suppository differs from the average weight by more than 10%.

#### Chemical testing

##### Disintegration test

In disintegration test [15,16] apparatus disintegration time of suppositories are measured placing suppositories in each tube and the basket rack assembly is positioned in a 1-litre beaker of water or simulated gastric fluid or simulated intestinal fluid at 37°C±2°C such that the suppository remains 2.5 cm from the bottom of the beaker. Standard motor moves [17] the basket up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 CPM (cycles per minute). USP disintegration test will be passed if all the suppositories disintegrate and the particles passed through the #10 mesh screen within the specified time.

##### Dissolution testing

Dissolution testing [18] is often required for suppositories to test for hardening and polymorphic transitions of active ingredients and suppository bases. Dissolution testing methods include the paddle method, basket method, membrane diffusion method/dialysis method, and the continuous flow/bead method. In vitro dissolution study is performed by using USP Type I/II Apparatus. The suppository is kept in 900 ml of dissolution fluid phosphate buffer pH 7.4 or phosphate buffer pH 6.8 or 0.1N HCl (pH 1.2) or simulated gastric fluid and stirrer rotating at specified rpm and maintaining the temperature 37±0.5°C of dissolution media [19, 20]. 5 ml of samples were withdrawn at different time intervals replaced with fresh medium and analyzed in UV-Visible spectrophotometer for estimation of absorbance taking a suitable blank solution. Finally, the drug release rate is calculated using suitable equation.

##### Content uniformity testing [21]

In order to ensure content uniformity, individual suppositories must be analyzed to provide information on dose-to-dose uniformity. Testing is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set. "Acceptance value calculations are not required for suppositories.

Assay 10 units individually as directed in the Assay in the individual monograph, unless otherwise specified in the *Procedure for content uniformity*"

The USP 30 "Criteria" 17 for suppositories states the following:

**Limit A** (if the average of the limits specified in the potency definition in the individual monograph is 100.0% or less) – Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in each of the 10

dosage units as determined from the Content Uniformity method lies within the range of 85.0% to 115.0% of the label claim, and the RSD is less than or equal to 6.0%. If 1 unit is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, or if the relative standard deviation is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if the not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim and the RSD of the 30 dosage units does not exceed 7.8%.

**Limit B** (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent). If the average value of the dosage units tested is 100.0

percent or less, the requirements are as in Limit A. If the average value of the dosage units tested

is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under Limit A, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100.

If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under Limit A, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100.

#### Aging and aging tests

Changes over time [22] may alter the physical and/or chemical properties of a suppository. Melting point fluctuations, for example, may occur either as a result of polymorphic changes in the excipient, in which case the temperature variation will be between 1 and 1.5°C maximum or as a result of evaporation of a volatile medicament or because of physical or chemical reactions between medicaments or excipients.

#### CONCLUSION

Quality control test for rectal dosage form can provide necessary information to develop qualitative products. Rectal administration can have a potential drug delivery system particularly for drugs that are either too irritating for the gut or more effective when not metabolized by the liver. Suppositories offer patients an option that is less invasive and less discomforting.

#### REFERENCES

- Lachman L, Lieberman AH et al. The Theory and Practice of Industrial Pharmacy CBS Publishers and Distributors. New Delhi. 2009; 564-588.
- Boylan CJ, Swarbrick J et al. Encyclopedia of pharmaceutical technology. 2002; 1 (2): 932- 955.
- Swamy PV, Ali M.U, Anandkumar Y et al. Design and evaluation of Rectal Drug Delivery Systems of Non-Steroidal anti-inflammatory drug. International Current Pharmaceutical Journal. 2012; 1 (7): 165-170.
- Yousif HS et al. Formulation of Tinidazole Rectal Suppositories. Asian Journal of Pharmaceutical Sciences. 2011; 10(2): 69-83.
- Gowthamarajan K, Venketeshwaran G, Suresh B. et al. Formulation and Evaluation properties of Meloxicam Solid dispersion incorporated Suppositories. Indian Journal of Pharmaceutical Science. 2002; 2(4): 525-528.
- Pushkar Baviskar P, Jaiswal SK, Sadique S, Landged A. Formulation and Evaluation of Lornoxicam Suppositories, The pharma innovation – journal 2013; 2(7):20-28.
- Coben LJ, Lordi NG. Physical stability of semisynthetic suppository bases. J Pharm Sci.1980;69: 955–960.
- Kaewnopparat S, Kaewnopparat N. Formulation and Evaluation of Vaginal Suppositories Containing Lactobacillus. World Academy of Science, Engineering and Technology 2009; 55:640-643.
- Setnikar I, Fantelli S. Liquefaction time of rectal suppositories. J Pharm Sci. 1962; 51: 566–571.
- Gold M, VePuri Murti Block LH. Suppository development and production. In: Lieberman HA Rieger MM Banker GS eds. Pharmaceutical Dosage Forms: Disperse Systems, New York Marcel Dekker 1996;2: 447–496.
- Saleem MA, Taher M, Sanaullah S. et al. Formulation and evaluation of Tramadol Hydrochloride Rectal Suppositories. International Journal of Pharmaceutical Science. 2008; 2(5): 641-645.
- Azhgikhin IS. Determination of the hardness of suppository bases using Kaminski's device. Aptechn Delo 1965; 14:14–19.
- Gjellan K, Graffner C. Comparative dissolution studies of rectal formulations using the basket, the paddle and the flow-through methods. I. Paracetamol in suppositories and soft gelatin capsules of both hydrophilic and lipophilic types. Acta Pharm Nord 1989; 1: 343–354.
- El-majri M, Sharma RK et al. Formulation and Evaluation of Piroxicam Suppository. International Journal of Drug Delivery. 2010; 1(2): 108-112.
- Furuno K, Gomita Y, Yoshida T, Oishi R, Saeki K, Araki Y. In vivo and in vitro release of indomethacin from water-soluble and fatty base suppositories. Acta Med Okayama 1992; 46: 223–231.
- Kale VV, Trivedi RV, Sanjay P. Development and evaluation of a suppository formulation containing lactobacillus and its application in vaginal diseases, Ann. N.Y. Acad. Sci. 2005;1056: 359-365.
- Schobel H, Klaus T, Raguse U, Pfliegel P. The determination of the real dissolution rate of drug substances in melted suppository masses. Pharmazie 1988; 43: 650–651.
- Janicki S, Sznitowska M, Zebrowska W, Gabiga H, Kupiec M. Evaluation of paracetamol suppositories by a pharmacopoeial dissolution test – comments on methodology. Eur J Pharm Biopharm 2001; 52:249–254.
- Nair L, Bhargava HN. Comparison of in vitro dissolution and permeation of fluconazole from different suppository bases. Drug Dev Ind Pharm 1999; 25:691–694.
- Koch HP, Klissenbauer C, Ritzinger A, Wallentin A. In vitro studies of drug liberation from suppositories with the rotating flask method. Pharmazie 1987;42:169–172.
- Anon U.S. Pharmacopeia 30–National Formulary 25. Rockville, MD U.S. Pharmacopoeial Convention 2007.
- Sah LM, Saini RT et al. Formulation development and release studies of indomethacin suppositories. Indian journal of pharmaceutical sciences. 2008; 70(4): 498-501.

© 2017 by the authors; licensee MJPMs, India. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (<http://creativecommons.org/licenses/by/4.0/>).