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Formulation and Evaluation of Sustain Release Metformin Tablets by Wet Granulation Method for Enhanced Patient Compliance

Mr. Kailas B. Gore*, Miss. Nandini Patil, Dr. Megha T. Salve

Shivajirao Pawar College of Pharmacy, Pachegaon , Ahilyanagar, 413725

ABSTRACT:

By using the wet granulation process, sustained release tablets of metformin were successfully made using a variety of polymers, including xanthan gum and Karaya gum. There were no compatibility issues with the excipients utilized in the trial, according to preformulation tests for drug excipient compatibility. In order to provide a controlled release of the medication, guarantee long-lasting therapeutic benefits, and minimize the frequency of dose, the goal of this study was to develop and assess metformin hydrochloride sustained-release tablets. Using hydroxypropyl methylcellulose (HPMC) as a rate-controlling polymer and other excipients such microcrystalline cellulose (MCC), magnesium stearate, and povidone, sustained-release formulations of metformin were created.

Direct compression was used to create the tablets, which were then examined for a number of physical and chemical characteristics. For MET to increase patient compliance and extend its duration of action, SR products are required. Formulation scientists have faced difficulties in developing oral sustained release systems since they are unable to confine and localize the system at certain gastrointestinal tract locations. Tests for weight fluctuation, hardness, friability, thickness, dissolution, content uniformity, and assay were all part of the post- compression evaluation. The toughness of the tablets was ensured by their uniform weight fluctuation (±5% of the average weight), acceptable hardness (8–10 kg), and minimum friability (0.4% weight loss). The thickness (4.5 mm ±5%) was constant.

With 12.5% of the medication released in the first hour and 92% after 8 hours, the dissolving trials showed a regulated release profile, suggesting that the tablets offer a gradual release of the medication.

Keywords: Metformin hydrochloride, SR matrix tablet, HPMC, Wet granulation technique

Introduction :

Diabetes mellitus, a chronic metabolic disease that affects more than 463 million people globally, is typified by elevated blood sugar levels. A common oral antidiabetic drug, metformin hydrochloride, lowers the liver's synthesis of glucose and improves insulin sensitivity to help regulate blood sugar levels (1). But because metformin hydrochloride has a short half-life and needs to be taken several times a day, patients may not take it as prescribed. By lowering the frequency of dose and preserving a steady therapeutic impact, sustained release tablets can offer a practical and efficient means of enhancing patient compliance (3).

In order to achieve therapeutically appropriate drug concentrations in the systemic circulation over a prolonged period of time1, sustained-release (SR) oral delivery systems were developed. SR matrix tablets have contributed to a new advancement in pharmaceutical science.

Dosage forms that release the drug continuously and continuously for a suitable amount of time keep the concentration of the drug in the plasma at a therapeutic level. medication preparations that alter the rate of medication absorption to lessen the incidence of dosage have been on the market for a long time. Due to their ease of use and formulation, matrix tablets are the most commonly used dosage form for oral sustained release (SR). The matrix system is a release mechanism that regulates and extends the release of a medication that has been dissolved or distributed. Actually, a matrix is a well complex of one or more medications and a gelling agent, such as hydrophilic polymer 4-6. An estimated 300 million individuals will live there by 2025. (4)

Strong cation-exchange resins, indion 244 and 264, were used in a complexation technique in an effort to both conceal the bitter taste and maintain the release of metformin HCl. Drug loading onto ion-exchange resin was optimized for temperature, drug:resin ratio, activation, mixing time, pH effect, and mixing method. XRPD and IR were used to describe the resinate and assess its micromeritic qualities and taste masking. Hydoxypropylmethylcellulose K100M was used to make resinate sustained release tablets. The tablets' hardness, thickness, friability, drug content, weight fluctuation, and in vitro drug release were all assessed.

. The resulting tablets (Batch B-6) had first order kinetics and a 10-hour sustained release of the medication. The diffusion of drug molecules through the polymeric material into the aqueous medium is regulated by the release of metformin HCl from the resinate. As an alternative to the traditional tablet, the results demonstrated that metformin HCl could be effectively taste-masked and made into a sustained dosage form. long-term medication delivery system:

Drug delivery systems that are intended to produce a prolonged therapeutic effect by continuously releasing medication over an extended period of time following the administration of a single dose are referred to by the following terms: sustained release, sustained action, prolonged action, controlled release, extended action, timed release, and depot dosage form.

Depending on the formulation's residence period in the GIT, an effect from an oral sustained-release dose form lasts for many hours (5).

Properties :

1) Properties Physical

1. Appearance: White to off-white, oval-shaped tablets
2. Size: 12-15 mm in length, 6-8 mm in width, and 4-6 mm in thickness
3. Weight: 500-600 mg
4. Hardness: 10-15 kg/cm²
5. Friability: Less than 1%
6. Disintegration Time: More than 12 hours

2) Pharmacological Properties:

1. Mechanism of Action: Decreases glucose production in the liver, increases insulin sensitivity, and enhances glucose uptake in muscles .
2. Therapeutic Class: Biguanide antidiabetic agent

3) Pharmacokinetic Properties:

1. Absorption: Slowly and incompletely absorbed from the gastrointestinal tract.
2. Bioavailability: 50-60%.
3. Peak Plasma Concentration: 2-4 hours.
4. Elimination Half-Life: 4-8 hours.
5. Excretion: Excreted unchanged in the urine.

4) Therapeutic Properties

1. Indications: Type 2 diabetes mellitus.
2. Dosage: 500-2000 mg/day, administered orally with meals.(6)
3. Efficacy: Improves glycemic control, reduces hemoglobin A1c levels, and decreases the risk of cardiovascular events.
4. Safety: Generally well-tolerated, but may cause gastrointestinal side effects, lactic acidosis, and hypoglycemia.

5) Stability Properties

1. Shelf Life: 2 years from the date of manufacture.
2. Storage Conditions: Store in a cool, dry place, away from light.
3. Packaging: Store in a tightly closed container, protected from moisture.

Advantages: .

1. Better Flow Properties: The powder mixture's flow characteristics are enhanced by the wet granulation process, which facilitates tablet compression.
2. Enhanced Tablet Strength: By creating solid links between the particles, the wet granulation process contributes to an improvement in tablet strength.
3. Less Dustiness: The powder mixture is easier to handle and process when the wet granulation method is used since it is less dusty.
4. Better prolonged Release Properties: By creating a robust matrix that delivers the medication gradually, the wet granulation process helps to improve the tablets' prolonged release qualities.
5. Economical: In contrast to other granulation techniques, the wet granulation method is economical.

Disadvantages:

1. Time-consuming Process: Mixing, granulating, drying, and milling are some of the procedures involved in the wet granulation method, which takes a long time.
2. Needs Solvents: The wet granulation process necessitates the use of solvents, like ethanol or water, which may be an issue for certain medications that are moisture-sensitive.
3. Danger of Over-Granulation: The wet granulation technique may result in over-granulation, which could produce tablets that are excessively dense or hard. (7)

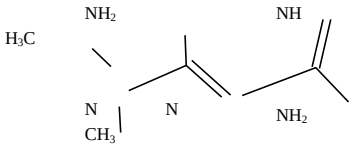
Drug profile: Metformin

Generic name: Metformin

IUPAC Name: N,N-Dimethylimidodicarbonimidic diamide

Molecular Formula :C4H11N5

Molecular Weight : 129.16 g/mol Structural formula Structural formula:



Mechanism action of metformin:

1. Reducing Glucose Production in the Liver: By lowering the activity of enzymes involved in gluconeogenesis, metformin prevents the liver from producing glucose.
2. Improving Insulin Sensitivity: Metformin makes muscle and fat cells more sensitive to insulin, which facilitates the easier uptake of glucose by these cells.
3. Improving Muscle Glucose absorption: Metformin decreases blood glucose levels by increasing muscle absorption of glucose (8).

Table No 1 : Formulation Table of metformin

Sr. No	Ingredients (Mg)	F1	F2	F3	F4	F5
1	Metformin	500	500	500	500	500
2	Polyethylene oxide *****	100	125	150	175	200
3	Starch	150	125	100	75	50
4	Ethyl cellulose	20	20	25	30	35
5	Dicalcium Phosphate	100	100	100	100	100
6	Steric acid **	5	5	5	5	5
7	Polyethylene glycol*	5	5	5	5	5
8	Magnesium trisilicate*	5	5	5	5	5

Material and method:

Zim Laboratories (Nagpur, India) provided a free sample of metformin hydrochloride-IP. We purchased Indion 244 and Indion 264 from Ion Exchange India Ltd. in Mumbai, India. We purchased HPMC (K100M) and MCC (PH 102) from Loba Chemie in Mumbai, India. High analytical quality was employed for all other compounds and reagents. Pharmaceuticals Ltd., India's New Delhi. We bought magnesium stearate, polyvinyl pyrrolidone K30, and hydroxy propyl methyl cellulose from Himedia Chem. Lab in Mumbai. We bought talc, sodium alginate, and starch from Mumbai's Loba Chemicals Pvt. Ltd. The HPLC-grade acetonitrile, methanol, and isopropyl alcohol were provided by Merck Ltd. in India. The remaining ingredients were all analytical grade. In-house triple-distilled water was produced. (9)

Preformulation studies:

1 *)* Physical characteristics

The quality of tablet, once formulated by rule, is generally dictated by thequality of physicochemical properties of blends.The various characteristics of blends tested as per Pharmacopoeia.

Solubility :

Solubility of the drug was determined by taking some quantity of drug (about 10 mg) in the 10 ml volumetric flasks separately and added the 10 ml of the solvent (water, ethanol, methanol, 0.1N HCL, 0.1N NaOH, chloroform and 7.4 pH buffer) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

Point of melting A fusion tube was filled with a tiny amount of particles. That tube holding castor oil was put in the Chemline, a device that determines melting points. The castor oil's temperature was automatically raised gradually while monitoring the temperature at which the powder began to melt and the temperature at which it had completely melted. (10)

FTIR spectroscopy

The sample's KBr concentration ought to fall between 0.2% and 1%. A lower concentration in the sample is necessary since the pellet is much thicker than a liquid layer (Beer's Law). About 80 mg of the combination is required for the die set you will be using. Getting clean pellets is usually difficult when too much attention is paid to it. The materials' FTIR spectra were captured using 20 scans with a resolution of 4 cm-1 throughout a spectral range of 4700 to 400 cm-1.

MET MET's λ max was determined by precisely weighing 100 mg into a 100 ml volumetric flask, dissolving it in distilled water, and then adding more distilled water to make up the volume. Using methanol as the volume and markings, pipette 1 ml of this solution into a 10 ml volumetric flask.

as stock. Make a suitable dilution to reduce the concentration to 2–12 µg/ml. To find the absorption maximum (λ max), the resultant solution is scanned in the 200–400 nm range using a UV spectrophotometer (UV-1700 Shimadzu corporation, Japan). A graph of concentration vs absorbance was displayed. (11)

Micromeritics properties:

Angle of repose :

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2cm above graph paper that is placed on a flat horizontal surface.

$\theta = \tan^{-1}(h/r)$

Where, θ is the angle of repose, h is height of pile; r is radius of base of the pile.

Bulk density (BD) *:*

Each formula's precisely weighed powder blend was added to a measuring cylinder after being gently shaken to break up any agglomerates that might have developed. Bulk volume was determined by measuring the volume occupied by the powder. The following formula was used to calculate the BD of powder mixtures.

Bulk density = Total weight of powder/Total volume of powder

Measures of powder compressibility:

Carr’s Index = [(tap - b) / tap] × 100 Where, b = Bulk Density

Tap = Tapped Density

Tapped bulk density (TBD)

Each formula's precisely weighed powder blend was added to a measuring cylinder after being gently shaken to break up any agglomerates that might have developed. The tapped volume was obtained by tapping the measuring cylinder until no more volume change was seen. The following formula was used to calculate the TBD of powder mixtures.

TBD = Total weight of powder/Total volume of tapped Powder.(12)

Evaluation of Post Compression Parameters:

1) Disintegration Test

Determining if the sustained release Metformin tablets can retain their physical integrity and release the active component in a controlled manner is the aim of the disintegration test.

• **Approach**:

A disintegration tester, which holds the tablets in a mesh screen or basket, is usually used to conduct the disintegration test. After that, the tester is submerged at a regulated temperature in a dissolution medium, such as water or buffer solution.

Weight variation:

Twenty pills were chosen at random, weighed, and their average weight was compared to the weight of each individual tablet. The weight variation as a percentage was computed. In accordance with Indian Pharmacopoeial specifications, tablets weighing between 80 and 250 mg on average should have a percentage deviation of no more than ± 7.5%, while tablets weighing more than 250 mg should not have a departure of more than ±5%.

Friability test:

Twenty tablets were chosen at random, and after having their surfaces scrubbed with a hair brush to get rid of any dust that might have adhered, they were weighed and put in the friabilator (Electro Lab USP EF-2). After that, they were free to fall 100 times from a height of 6 inches while moving at 25 rpm for four minutes. After that, the tablets were weighed and powdered. Weight loss as a percentage was calculated for any weight loss brought on by fracture or abrasion. Each formulation's replicate determinations were averaged. The following formula was used to determine friability. (13)

F=(W0-W)\W

F = Friability, W = Final weight, Wo = Initial weight

Hardness test:

The Monsanto Hardness tester was used to measure the tablets' hardness. The unit of measurement is kg/cm². From each formulation, ten pills were chosen at random, and the mean and standard deviation were determined.

Uniformity of thickness:

A digital vernier caliper was used to measure the tablet's thickness and diameter, which were crucial for consistency in tablet size. Twenty tablets, each weighing the same as 10 milliliters of water in 100 for 10 minutes, were taken, and the resulting solution was filtered using phosphate buffer, which was then measured by the same sol standard and samp spectrophotometer using methanol as a blank.

In vitro dissolution test:

- The market sample for in vitro dissolving was apparatus II (paddle) HCl. Samples were taken at 10-ml intervals and replaced with medium at 37 ± 2°C. The percentage of drug concentrations in the samples was then analyzed.

All of the manufactured tablets and the market sample underwent an 8-hour in vitro dissolution study using USP dissolution equipment II (paddle) at 37 ± 2°C and 100 rpm in 900 ml of 0.1 N HCl. To keep the volume consistent, a 10-milliliter sample was taken out at pre-arranged intervals and replaced with the same amount of dissolving media (37 ± 2°C). The UV-Visible Spectrophotometer was used to analyze the solution samples. The drug concentrations were used to calculate the percentage of drug dissolved. (14)

- **Zero Order Kinetics**

Zero Order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system[93] The following equation is used to express the model

Q Q) +Kot

Where, Q is the amount of drug dissolved in time t

Q) is the initial amount of drug in the solution Ko is the Zero Order release constant

For practical purposes the equation is rearranged:

Percentage of drug release$=K_t$

- **First Order Kinetics**

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior. The following equation is used to express the model

log Qt = log QO + Kt/ 2.303

Where, Q is the amount of drug dissolved in time t

Q) is the initial amount of drug in the solution K is the First Order release constant

For practical purposes the equation is rearranged:

Log percentage of drug unreleased Kt/2.303

- **Formulation Procedure Step 1: Pre-formulation Study**

1. Weighing: Weigh 100g of Metformin Hydrochloride.
2. Sieving: Sieve the Metformin Hydrochloride through a #40 mesh sieve.
3. Determination of Particle Size: Determine the particle size of the sieved Metformin Hydrochloride using a particle size analyzer.

Step 2: Excipient Selection

1. Selection of Polymer: Select a suitable polymer (e.g. HPMC, EC) for sustained release.
2. Selection of Filler: Select a suitable filler (e.g. lactose, microcrystalline cellulose) for sustained release.
3. Selection of Lubricant: Select a suitable lubricant (e.g. magnesium stearate) for sustained release.

Step 3: Formulation Design

1. Formulation Design: Design the formulation using a suitable ratio of Metformin Hydrochloride to excipients.
2. Calculation of Excipient Amounts: Calculate the amounts of excipients required based on the formulation design.

Step 4: Granulation

** 1. Wet Granulation: Granulate the powder blend using a wet granulation method.

2. Dry Granulation: Granulate the powder blend using a dry granulation method.

Step 5: Compression

1. Compression: Compress the granules into tablets using a tablet press.
2. Tablet Weight: Control the tablet weight to ensure uniformity.(15)

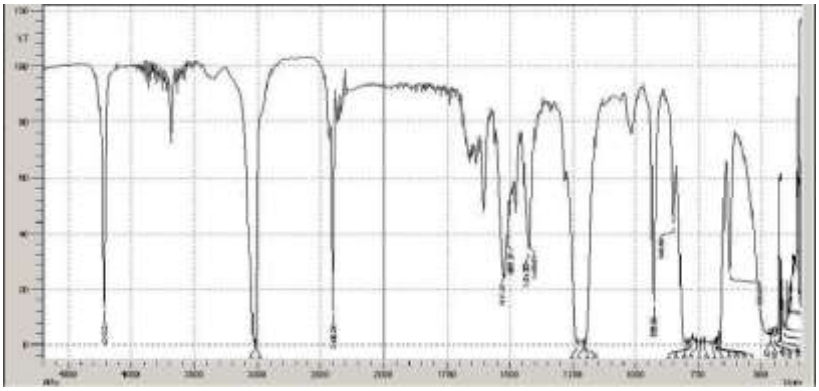
Result and discussion:

It was discovered that the pure medication MET had a melting point between 223 and 226°C. While MET was insoluble in acetone, it was easily soluble in water and very weakly soluble in methanol and ethanol. FTIR spectroscopy was used to identify MET in relation to the marker component. According to specification Figure 1, it was determined from the IR spectrum result. In the concentration range of 2–12 µg/ml at 234 nm, the MET calibration curve was determined to be linear. 2. The funnel method was used to calculate the angle of repose. The cylinder method was used to obtain the bulk and tapped densities, and the following formula was used to determine Carr's index (CI). —100/TBD = (TBD-LBD) is Carr's index.

Powder flow characteristics could be predicted using Hausner's ratio, which was connected to interparticle friction. It was believed that the produced granules' Hausner's value, which varied from 1.15 to 1.16, indicated good flow qualities. Table 2. According to Table 3's statistics, all tablet formulations' physical characteristics, tablet hardness, friability, weight fluctuation, and drug content homogeneity were determined to be satisfactory and repeatable. Based on the compression force used, tablet hardness was found to be good (between 6 and 8 kg/cm2).

Friability was below 0.5 percent (wt/wt). Wet granulation is a suitable technique for creating high-quality matrix tablets of metformin HCl, as evidenced by the produced tablets' low weight fluctuation and high degree of drug content homogeneity. First, HPMC K4M (F1) was used to make the tablets, which released 40.61% and 81.23% of metformin HCl in 1 and 4 hours, respectively. Additionally, 81.01% of the medication was released from the HPMC K15M (F2) tablets in 4 hours. The release of metformin HCl is retarded by 36.11%, 73.65%, and 93.44 at 1 hour, 4 hours, and 8 hours, respectively, by the tablets made with K100M (F3), drug-to-polymer ratios of 5:2, and isopropyl alcohol as a granulating agent.. F3 formulation has showed an optimal formulation due to its closest profile to the target in terms of release

Figure no 1: FT-IR spectrum of pure drug (MET)



Preformulation parameters:

The results of the evaluation are presented in the following tables Table no :2 Wet Granulation

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	27.08	0.58	0.69	15.94	1.18
F2	25.12	0.48	0.57	15.78	1.18
F3	26.45	0.54	0.65	16.92	1.2
F4	26.12	0.56	0.66	17.65	1.06
F5	25.45	0.54	0.62	17.54	1.17

A variety of pre-formulation parameters were applied to the tablet powder mixture. The powder blend's good flow qualities are indicated by the angle of repose readings. All of the formulations' bulk densities were determined to be between 0.48 and 0.58 (gm/cm3), indicating that the powder has satisfactory flow characteristics. All of the formulations' tapped densities fell between 0.57 and 0.69, indicating that the powder had adequate flow characteristics. All of the formulations' compressibility indices ranged from 14 to 18, indicating that the powder had good flow characteristics. The powder's good flow qualities are shown by the Hausner ratio, which ranges from 0 to 1.25 in all formulations.

3. : EVALUATION OF PHYSICAL CHARACTERISTICS OF TABLETS :

The results of the evaluation are presented in the following tables Table no 3:

Test	**Specification**	**Result**	**Acceptance Criteria**
Weight Variation	Average weight of tablets	500 mg	±5% of the average weight
Hardness	Measured using a hardness tester	8–10 kg	6–12 kg
Friability	Loss in weight after testing	0.5%	<1%
Thickness	MeasuSSred with a micrometer	4.5 mm	±5% variation from average
Dissolution (1 hr)	Cumulative release of Metformin	15%	NLT 12% in 1 hr
Dissolution (8 hrs)	Cumulative release of Metformin	90%	85-95% (sustained release)
Content Uniformity	% of Metformin in each tablet	98.5%	95-105%
Assay	% of active ingredient	99.2%	95-105%

CONCLUSION

All of the post-compression evaluation tests showed satisfactory outcomes for the sustained-release Metformin pills. The tablets were a good formulation for controlled drug delivery because they satisfied the necessary requirements for weight fluctuation, hardness, friability, thickness, dissolving, and content consistency. According to the dissolution data, Metformin was released in a controlled way and had the intended therapeutic effect for a long time. Several polymers are used in the current study's sustained release matrix formulation of metformin. First, the drug molecule's analysis method was developed. Using varying concentrations, absorption maxima were identified and a calibration curve was created. The formulation was created utilizing a variety of polymers, including Xanthan and Karaya gum.

Several preformulation studies were conducted on the formulation blend, and all of the formulations were found to have satisfactory flow properties, suggesting that the powder blend had high flow capabilities. Of all the formulations made with Karaya gum, one was able to delay the release of the medication for up to 12 hours. Therefore, that was not taken into account in those formulations. Xanthan gum-prepared formulations delay the release of less medication for up to 12 hours. Direct compression tablets had the highest drug release of any formulation, although wet granulation tablets had the highest hardness. The F2 formulation was thought to be the most optimized of all the formulas. At 12 hours, the drug release was 96.61%.

References

1. International Diabetes Federation. (2020). IDF Diabetes Atlas, 10th edition.
2. Bailey, C. J., & Day, C. (2019). Metformin: its role in type 2 diabetes treatment. Diabetes, Obesity and Metabolism, 21(1), 5-15.
3. Liu, F., et al. (2019). Patient preferences for oral antidiabetic medications in type 2 diabetes: a
4. 4.systematic review. Diabetes, Obesity and Metabolism, 21(1), 16-26 Chowdary P, Sravani T, Basheeruddin MD. Formulation and evaluation of sustained release tablets of nateglinide by using natural polymers. Int J Adv Pharm Sci. 2017; 9(1):8-13. https://doi.org/10.5138/09761055.2065
5. Sharma BK. Instrumental methods of chemical analysis. 23rd ed. New Delhi: Goel Publishing House; 2004. p. 123
6. United States Pharmacopeia (USP). (2020). Metformin Hydrochloride Tablets.
7. Indian Pharmacopoeia. (2018). Metformin Hydrochloride Tablets.
8. Rowe, R. C., et al. (2012). Handbook of Pharmaceutical Excipients. Pharmaceutical Press.
9. Pentikainen PJ. Bioavailability of metformin comparison of solution, rapidly dissolving tablet, and three sustained release products. Int J Clin Pharmacol Ther Toxicol. 1986; 24:213-220.
10. Brahmankar DM, Jaywalk SB. Biopharmaceutics and Pharmacokinetics Pharmacokinetics, 2nd Ed. Vallabh Prakashan, Delhi, 2009:399-40
11. Patel AN, Rai JP, Jain DK, Banweer JI. Formulation, development and evaluation of cefaclor extended release matrix tablet. Int J
12. Pharm Pharm Sci. 2012; 4(4):355-7
13. Lee V. H., Robinson J. R. in ,“Sustained and Controlled Release Drug Delivery System ” Marcel Dekker, New York, p.no. 71-121.,138-171.
14. T. Sivannarayana , I. John Noble Devakumar Sk. Saddam Hussain K. Phani Jithendra K. Prakash.Formulation and Evaluation of sustained release Troxipide Matrix Tablets for Twice
15. Daily.Int. J. Drug Dev. & Res., 2013, 5 (3): 396-402
16. Indian Pharmacopoeia. (2018). Metformin Hydrochloride Tablets.
17. Rowe, R. C., et al. (2012). Handbook of Pharmaceutical Excipients. Pharmaceutical Press.