# CHAPTER – IV

# AIM AND OBJECTIVE

## 4.1 AIM

The present research is aimed at **"Design and Characterization of Drug Delivery System using Hot Melt Coating Technique."** This involves the application of Hot Melt Coating (HMC) for

A. Taste Masking of Tenofovir Disoproxil Fumarate (TDF)
B. Improvement in Stability of Sitagliptin Phosphate Monohydrate (SPM)

## 4.2 Objectives

The important objectives of the proposed research work were,

1. Characterization of Tenofovir Disoproxil Fumarate (TDF) and Sitagliptin Phosphate Monohydrate (SPM) API.
2. Designing the manufacturing process for a pre-determined aim.
3. Selection of raw materials.
4. Optimization and evaluation of Manufacturing Process Parameters.
5. Evaluation of the final product of Tenofovir Disoproxil Fumarate (TDF) for Taste Masking and Stability Improvement for Sitagliptin Phosphate Monohydrate (SPM).
6. Comparative Dissolution Assessment.
7. Stability Evaluation of Optimized Dosage Forms.

## 4.3 Quality Target Product Profile (QTPP)

**Part A:**

The QTPP for Tenofovir Disoproxil Fumarate Pellets and Tablets is outlined in the table below. The Quality Attributes identified as Critical Quality Attributes (CQAs) are also provided. The goal is to develop solid oral dosage form pellets and tablets. The objective is to investigate the potential of the Hot Melt Coating technique for Taste-masking when formulating either Pellets or Tablets. Taste masking for the pellets is particularly important for pediatric and elderly patients who have difficulty swallowing large tablets.[22, 23]

**Table 4.1 : Quality Target Product Profile (QTPP) for TDF Pellets and Tablets**

| QTPP Elements | Target (Pellets) | Target (Tablets) |
|---|---|---|
| Dosage form | Pellets (in Sachets) | Tablets (in Bottles) |
| Dosage design | Immediate Release | Immediate Release |
| Route of administration | Oral | Oral |
| Dosage Strength | 300 mg | 300 mg |
| Stability | At least 24 months at room temperature | At least 24 months at room temperature |
| Drug product Quality attributes | Physical attributes | Physical attributes |
| | Taste-masking (Bitterness) | Taste-masking (Bitterness) |
| | Assay | Assay |
| | Dissolution | Dissolution |
| Container closure system | Suitable for product stability | Suitable for product stability |

**Part B:**

The QTPP for Sitagliptin Phosphate Tablets 50mg (SPM)is defined in the following table. The quality attributes that were identified as drug product Critical Quality Attributes (CQAs) are also given below. The target is to formulate a Hot Melt Coated Tablets. The aim is to explore the potential of the hot melt coating technique for stability enhancement.[22,23]

**Table 4.2 : Quality Target Product Profile (QTPP) for SPM Tablets**

| QTPP Elements | Target |
|---|---|
| Dosage form | Hot Melt Coated Tablets |
| Dosage design | Immediate Release |
| Route of administration | Oral |
| Dosage Strength | 50 mg |
| Stability | At least 24 months at Room Temperature |
| Drug product Quality attributes | Physical attributes |
| | Moisture uptake |

| QTPP Elements | Target |
|---|---|
| | Assay |
| | Dissolution |
| Container closure system | Suitable for product stability |

### 4.4 Critical quality attributes

The Drug Product Critical Quality attributes of the drug products were identified[24] as below-

**Part A:**

**Table 4.3 : Critical Quality Attributes of TDF Pellets**

| Drug Product Quality Attributes | | Target | Is this CQA? | Justification |
|---|---|---|---|---|
| Physical Attributes | Appearance | White to off-white coated pellets | No | For better patient acceptance and compliance with treatment regimens, the target for pellet size is set. Formulation and process variables do not impact appearance. The size of pellets is controlled by fixing the screen sizes. Hence, it is not critical. |
| | Size | Easily swallowable | No | |
| | Taste | No Bitter taste | Yes | Affects patient acceptability, hence it is Critical. |
| Assay | | 95-105% | Yes | Assay variability will affect safety and efficacy and is influenced by process variables. |
| Dissolution | | NLT 80% (Q) in 30 minutes | Yes | Failure to meet the dissolution specification may impact on therapeutic efficacy.<br><br>Both formulation and process variables may affect dissolution. |

**Table 4.4 : Critical Quality Attributes of TDF Tablets**

| **Drug Product Quality Attributes** | | **Target** | **Is this CQA?** | **Justification** |
|---|---|---|---|---|
| Physical Attributes | Appearance | White to off white tablets | No | Similar to marketed products. Formulation and process variables do not impact appearance and size. Hence, it is not critical. |
| | Size | Similar to marketed | No | |
| | Taste | No Bitter taste | Yes | Affects patient acceptability, hence CQA. |
| Assay | | 95-105% | Yes | Assay variability will affect safety and efficacy and is influenced by process variables. |
| Dissolution | | NLT 80%(Q) in 30 minutes | Yes | Failure to meet the dissolution specification may impact on therapeutic efficacy. Both formulation and process variables may affect dissolution. |

**Part B:**

**Table 4.5 : Critical Quality Attributes of Sitagliptin Phosphate Monohydrate Tablets**

| **Drug Product Quality Attributes** | | **Target** | **Is this CQA?** | **Justification** |
|---|---|---|---|---|
| Physical Attributes | Appearance | White to off-white tablets | No | Similar to marketed products. Formulation and process variables do not impact appearance and size. Hence, |
| | Size | Similar to | No | |

| Drug Product Quality Attributes | Target | Is this CQA? | Justification |
|---|---|---|---|
| | marketed | | it is not critical. |
| Assay | 90-110% | Yes | Assay variability will affect safety and efficacy and is influenced by process variables. |
| Moisture uptake | NMT 2% | Yes | Moisture uptake by the drug will result in degradation and loss of assay. |
| Dissolution | NLT 80% (Q) in 30 minutes | Yes | Failure to meet the dissolution specification may impact on therapeutic efficacy.<br>Both formulation and process variables affect dissolution. |

**References**


1. Costa C, Casimiro T, Corvo ML, Aguiar-Ricardo A. Solid dosage forms of biopharmaceuticals in drug delivery systems using sustainable strategies. Molecules. 2021 Dec 17;26(24):7653.
2. Qiu Y, Chen Y, Zhang GG, Yu L, Mantri RV, editors. Developing solid oral dosage forms: pharmaceutical theory and practice. Academic press; 2016 Nov 8.
3. Grekov MA, Kostyrko SA. A multilayer film coating with slightly curved boundary. International Journal of Engineering Science. 2015 Apr 1;89:61-74.
4. Han JH, editor. Innovations in food packaging. Elsevier; 2005 Jul 20.
5. Environmental Protection Agency. Clean Air Act. 1970.
6. General Industry OSHA Safety and Health Standards, CFR. 1976.
7. Rothrock DA, Cheetham HC. Hot-melt coating. US patent 228509.1942.

8. Salawi A. Pharmaceutical Coating and Its Different Approaches, a Review. Polymers (Basel). 2022 Aug 15;14(16):3318.
9. Falcon-Neyra L, Palladino C, Gómez ML, Soler-Palacín P, González-Tomé MI, De Ory SJ, Frick MA, Fortuny C, Noguera-Julian A, Moreno EB, Santos JL. Off-label use of rilpivirine in combination with emtricitabine and tenofovir in HIV-1-infected pediatric patients: A multicenter study. Medicine. 2016 Jun 1;95(24):e3842.
10. Chapman TM, McGavin JK, Noble S. Tenofovir disoproxil fumarate. Drugs. 2003 Aug; 63:1597-608.
11. Singh BN, Kim KH. Drug delivery-oral route. Encyclopedia of pharmaceutical technology. 2002;1.
12. Zaric BL, Obradovic M, Sudar-Milovanovic E, Nedeljkovic J, Lazic V, Isenovic ER. Drug delivery systems for diabetes treatment. Current pharmaceutical design. 2019 Jan 1;25(2):166-73.
13. Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. Drug Safety. 1994 Oct;11(4):223-41.
14. Hultström M, Roxhed N, Nordquist L. Intradermal insulin delivery: a promising future for diabetes management. Journal of diabetes science and technology. 2014 May;8(3):453-7.
15. Tieger E., Kiss V., Pokol G., Finta Z. Crystallisation of a salt hydrate with a complex solid form landscape. Cryst. Eng. Comm. 2017; 19:1912–1925.
16. Stofella NCF, Veiga A, Oliveira LJ, Montin EF, Andreazza IF, Carvalho Filho MAS, Bernardi LS, Oliveira PR, Murakami FS. Solid-State Characterization of Different Crystalline Forms of Sitagliptin. Materials (Basel). 2019 Jul 24;12(15):2351.
17. Pande V: An overview on emerging trends in immediate release tablet technologies. Austin Therapeutics 2016; 3: 1026.
18. Green J.B., Bethel M.A., Armstrong P.W., Buse J.B., Engel S.S., Garg J., Josse R., Kaufman K.D., Koglin J., Korn S., et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N. Engl. J. Med. 2015; 373:232–242.

19. Berger J.P., Sinharoy R., Pocai A., Kelly T.M., Scapin G., Kelly Y.G., Pryor A.D., Wu J.K., Eiermann G.J., Xu S.S., et al. A comparative study of the binding properties, dipeptidyl peptidase-4 (DPP-4) inhibitory activity and glucose-lowering efficacy of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin in mice. Endocrinol. Diabetes Metab. 2018; 1:1–8.

20. Remm F., Kränkel N., Lener D., Drucker D.J., Sopper S., Brenner C. Sitagliptin Accelerates Endothelial Regeneration after Vascular Injury Independent from GLP1 Receptor Signaling. Stem Cells Int. 2018; 2018:5284963

21. Doggrell S.A., Dimmitt S.B. Sitagliptin and other 'gliptins'—Why prescribe them? Expert Opin. Pharmacother. 2016;17:757–760.

22. U. S. Food and Drug Administration. Guidance for Industry: Q11 development and manufacture of drug substance. 2012.

23. Raw AS, Lionberger R, Yu LX. Pharmaceutical equivalence by design for generic drugs: modified-release products. Pharmaceutical research. 2011 Jul;28:1445-53.

24. Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products, part II: quality by design for topical semisolid products. The AAPS journal. 2013 Jul; 15:674-83.