wjpmr, 2024, 10(6), 244-253

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

FORMULATION AND EVALUATION OF MULTIPARTICULATE SYSTEM TO ENHANCE FORMULATION EFFICACY

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Article Received on 13/04/2024 **Article Revised on 03/05/2024** **Article Accepted on 23/05/2024**

ABSTRACT

Multiparticulate is an advanced drug delivery method that offers several features for the successful development of immediate-release and controlled-release formulations. To enhance the effectiveness of a formulation, multilayer formulations are repeatedly used to avoid chemical incompatibilities between the active pharmaceutical components and to make it possible to produce various dose forms with distinct drug release patterns. The pharmaceutical industry has shown substantial interest in the manufacture of multiparticulate dosage forms by the increasing compaction of loose powder layers. Multiparticulate dosage forms are suitable for the simultaneous delivery of two medications in succession, the segregation of two incompatible chemicals, and the development of a continuous release in a single layer of immediate release as the initial dose and the second layer as the ongoing dose. The quick-release layer of the multiparticulate acted as an initial dose, while the sustained-release layer maintained therapeutic levels of the medication in the bloodstream for a prolonged duration. To address common GI problems such as low yield, cross-contamination between layers, insufficient hardness, improper individual layer weight control, and layer separation, high-quality multiparticulate development, and production need to be carried out on polymer presses specifically designed for that use. Using a modified polymer layer may be the best way to make multi particulate dosage under GMP conditions, especially when a lot of dosage needs to be made.

KEYWORDS: Multi-particulate system, Pellitization, Immediate Release, Bottom spray, Sustained Release, Drug Delivery System.

INTRODUCTION

Oral medication administration has been the most common method of drug delivery. It is widely recognized as the most prevalent method of drug delivery because the physiology of the gastrointestinal tract provides greater latitude for dosage form formulation than most alternative routes. Oral administration has historically been the most practical and widely utilized method of drug delivery owing to its simplicity. It is commonly known that compared to quick-release formulations, variable-release dose forms of the same medication may offer one or more advantages.[1]

A controlled release drug delivery system keeps the medicine released at a predetermined pace for a certain amount of time, either locally or systemically. These systems aim to offer delivery profiles that are capable of achieving therapeutic plasma levels.[2] The properties of the polymer control the release of pharmaceuticals. Consequently, using these features may provide dosage forms that are well-defined and can be reproduced consistently.[3]

Multi-Particulate Drug Delivery[4]

There are different ways to make multiparticulates. Multiparticulates made by different methods need to be processed in different ways and have different features. Pelletization, granulation, spray drying, and spray congealing are some of these ways that can be put into larger groups. The drug particles could be stuck inside the multiparticulates or stacked on top of them. After that, these multiparticulates can be changed in a lot of different ways to get the drug release profile that is wanted.[5]

Coating them is one way to change the way drugs are released from multiparticulates. Coating multiparticulates is done to get useful coats, make them more stable chemically, improve their physical properties, and make them easier for patients to accept. Coats are made from a variety of polymeric covering materials. These consist of dry granules, molten

polymers, polymer solutions, and liquid polymer dispersions. Various coating types, including focused release, delayed release, pulsatile release, and sustained release (SR), can be used to accomplish various functions.[4,6]

The majority of multi-particulate drug delivery systems are oral formulations made up of several tiny, distinct units, each of which has a unique set of desired characteristics. In these systems, the dose of the substance is usually spread throughout several subunits, each of which is made up of thousands of spherical particles with diameters ranging from 0.05 to 2.00 mm. Hence, pharmaceutical formulations containing the active ingredient as several tiny, independent subunits are known as multiparticulate dosage forms. To administer the prescribed overall dosage, these subunits are encapsulated, compressed, or filled into a sachet or tablet. A multiple-unit system is composed of discrete particles known as multiparticulates.[7]

Pelletization

Pelletization is the process of converting a medication and excipient mixture into tiny, free-flowing spheres for oral drug administration. Uniform, spherical pellets provide several benefits over powders, granules, and single-unit dose forms, making them popular in the pharmaceutical sector. Sized between 100 and 2000 micrograms.[8]

Fig. no. 1: MCC pellets.

Pellets have a lower surface area to volume ratio than powders, resulting in improved flow and mixing qualities and, ultimately, more reliable dosing. With a need for more targeted dosage forms, their ability to be adjusted and optimized in order to properly regulate the release of medication from the dosage system is becoming increasingly important. Pellets provide superior plasma profiles and reduce the danger of dosage dumping compared to modified-release single-unit systems.

Previous investigations have reported on the compression and compaction behavior of pellets made of microcrystalline cellulose. MCC was selected as a filler in pharmaceutical aggregates. Pellets exhibited minimal fragmentation. Another significant feature of the MCC pellets was their porosity, which was linked to the tensile strength generated by unlubricated pellets and influenced the degree of densification and deformation the pellets experienced during compression.[9,10]

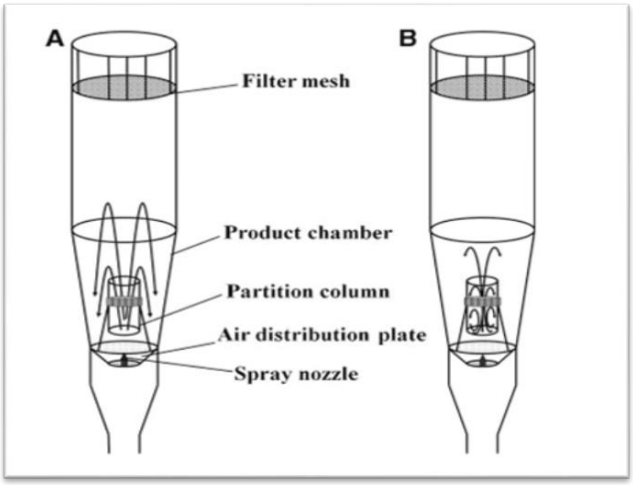


Fig. 2: Schematic representation of particle movement within the partition column of bottom spray fluid-bed coater.

Advantages of multiparticulate drug delivery system[11]

The focus of the study has been on this particular method of administering drugs because of its several advantages over traditional modes of administration. Some of these benefits include

• Enhanced gastric residence time that is predictable, and reproducible.
• Decreased variability among individuals and within individuals.
• Enhanced absorption of the drug in the body.
• Reduced negative effects and increased tolerance.
• Elimination of the risk of excessive drug release.
• The medication delivery method is designed to be versatile.
• Easy combination of pellets with different compositions or release patterns.
• Improved stability of the drug.
• Enhanced comfort and compliance for patients.
• Achievement of a distinct release pattern.

Drawbacks

• Excipients are required in proportionally increased quantities.
• Multiple formulation processes.
• Trained/skilled personnel required for manufacturing.
• Low drug loading.

Need of Multilayer[12]

• To manage the administration of dual-release fixed dosage combinations containing several active pharmaceutical ingredients (APIs).
• To create novel medication delivery methods, such as floating tablets for gastroretentive drug administration and buccal/mucoadhesive delivery systems. It helps control the rate of delivery of one or two active pharmaceutical ingredients (APIs).
• The goal is to increase a bilayer tablet's surface area by adding one or two inactive layers, which will operate as an erodible/swellable barrier to allow for the active component's controlled release.
• The features of one layer can be used to provide a controlled release of an API by mixing two incompatible APIs in a single dosage.

2. MATERIAL AND METHODS

2.1 Materials

Pellets was obtained from M B Sugars & Pharmaceuticals Pvt. Ltd. Pharmaceuticals exporter in Malegaon, (Maharashtra, India). Aceclofenac and paracetamol were obtained from Dhamtec Pharma and consultants Mumbai (Maharashtra, India). Ethanol was obtained from Variety traders Amravati (Maharashtra, India). HPMC and Ethyl cellulose were obtained from our own Institute P.R. Pote Patil college of pharmacy Amravati (Maharashtra, India).

2.2 Method of pellet Coating

Top spray: In the pharmaceutical industry, coatings are commonly applied to solid dosage forms such as tablets, pellets, or granules. The procedure is called Top spray coating. In a fluidized bed, particles are agitated and suspended before being sprayed with a coating solution. The top spray coating apparatus typically consists of a fluidized bed, one or more spray nozzles placed at the bed's top, an air supply mechanism, and a solution delivery structure.

Fig. no.3: ACG miniquest pellet coating machine.

An overview of the top spray coating mechanism is presented below

- To prepare the coating solution, dissolve Api, pigments, polymers, and other materials in a suitable solvent. The solution composition is carefully prepared to provide the desired coating attributes, such as colour, gloss, release profile, and mechanical strength.
- Fill the fluidized bed with tablets, pellets, or granules for coating. The bed is usually includes holes in it to let air pass through and dry the coated particles.
- Fluidized Bed Formation: Air is introduced from the bottom, and the coating solution is sprayed on the particles. The upward movement fluidizes the particles, keeping them afloat in the air and

preventing them from settling to the bottom of the bed.

- Drying and Solidification: When the suspended particles come into contact with the heated air stream, the coating solution's solvent evaporates. As the solvent evaporates, the polymer solids in the coating solution gradually settle onto the particle surface to form a homogenous coating layer. Furthermore, the coating is bound to the particle surface and solidified with the help of the drying process.
- End of Coating Process: Once the appropriate coating thickness and properties are achieved, the spray nozzles are turned off and the airflow is stopped. Before being transferred to another container or treated further, the coated particles are allowed to dry further in the bed[13].

3. RESEARCH METHODOLOGY

3.1 Pre-formulation Studies[14,16]

It is one of the important fundamentals in the development of any drug delivery system. Preformulation studies were performed on the drug, which included Appearance, solubility, pH, Solid state character, melting point determination, microscopy of Api, UV Spectroscopy, and FTIR spectroscopy.

1. Appearance

The active pharmaceutical ingredient was evaluated in terms of their physical form, colour, odor, texture, purity, and Packaging of the API.

2. Solubility

Solubility of the drug is the capacity to dissolve in a certain solvent, often water or lipids. Solubility affects the drug's absorption and bioavailability.

3. pH

The pH at which a drug molecule is in equilibrium between its ionized and unionized states. This affects medication absorption, distribution, and excretion, especially in acidic or basic conditions.

4. Solid state character

The solid-state characterization includes analyzing the API's crystal shape (polymorphism) and amorphous content.

5. melting point determination

These features refer to the drug's physical state (solid, liquid, or gas) at various temperatures.

6. Microscopy

Compound microscopy is commonly used to analyze Active Pharmaceutical Ingredient (API) powders for its ability to provide comprehensive information about particle shape, size distribution, and other characteristics.

7. UV spectroscopy

Compatibility with excipients was confirmed by carried out UV Spectroscopy. UV spectroscopy is used to determine the concentration of any unknown substance. UV-visible spectroscopy is a technique for investigating the absorption, transmission, and reflection of ultraviolet and visible light by substances. It gives useful information on the electronic structure and concentration of molecules in a sample, making it easier to identify, quantify, and characterize substances.

8. FTIR spectroscopy

Compatibility with excipients was confirmed by carried out FT-IR studies. FTIR spectroscopy (Fourier Transform Infrared) is a technique for determining the chemical composition of things by measuring the absorption of infrared light as it passes through a sample. It offers information on the sample's molecular structure, functional groups, and chemical bonds, which helps with material identification and characterization.

3.2 Evaluation parameters

3.2.1 Aceclofenac

1. Appearance

- **Physical form of API:** It is in fine crystalline powdery texture.
- **Color:** White to off-white.
- **Texture:** Fine or granular.
- **Odor:** No odor or faint characteristic odor.
- **Purity:** High purity, often exceeding 98% or even higher.
- **Storage:** Stored at a temperature 2-8^{o} C in an air-tight glass container protected from direct sunlight and moisture.

2. Solubility

- **Aceclofenac**

Aceclofenac is sparingly soluble in water but soluble in various organic solvents but more readily soluble in organic solvents such as ethanol 96%, methanol, acetone, chloroform, and dimethyl sulfoxide (DMSO).

3. Solid state character

- **Aceclofenac:** Aceclofenac typically forms crystals with defined edges and facets.

4. Melting point determination

The melting point of the aceclofenac was determined by the capillary method.

- Aceclofenac has a melting point of between 149 and 150°C.

5. Microscopy

- Microscopy of Aceclofenac Api was performed under a compound microscope and solid crystal-like appearance was observed under the microscope.

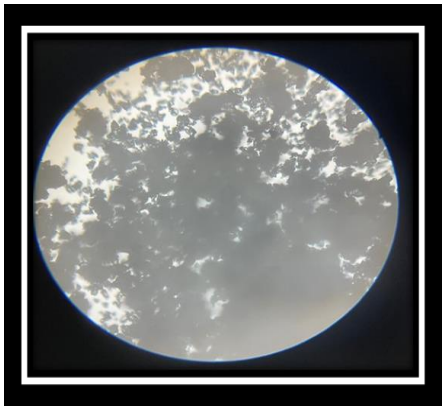


Fig. 4: Microscopy of Aceclofenac API.

6. UV spectroscopy

- **Preparation of stock and standard solution for the calibration curve of Aceclofenac**

A. Preparation of phosphate buffer 6.8 pH

Dissolve 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

B. Preparation of standard stock solution[1]

1. Weigh and transfer 0.10gm of aceclofenac in 100 ml of volumetric flask.
2. Add phosphate buffer 6.8 pH to make the volume up to 100ml in the volumetric flask.
3. Dissolve the drug in phosphate buffer. The concentration of that stock solution is 1000ug/ml.

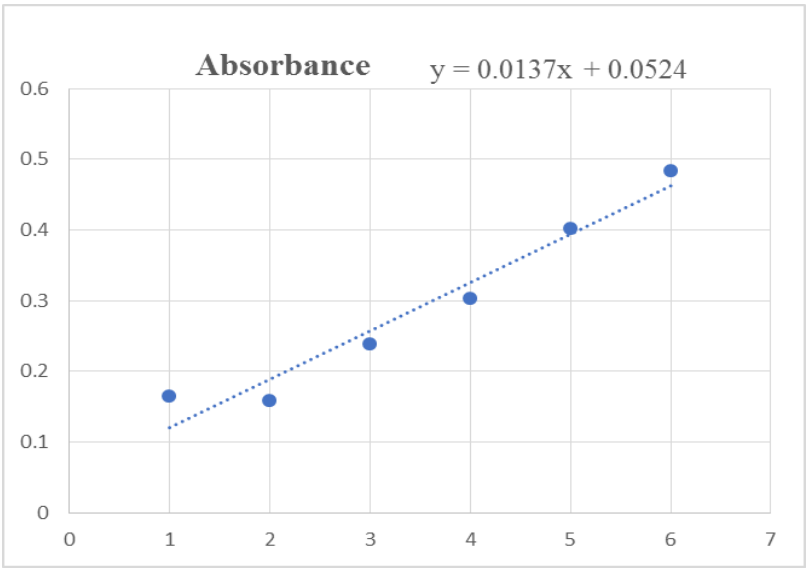
C. Preparation of stock solution[2]

1. Pipette out 10 ml of standard stock solution in 100 ml of volumetric flask.
2. Makqe the volume of 100 ml volumetric flask with phosphate buffer 6.8 pH.
3. The concentration of stock solution 2nd is 100ug/ml.

D. Dilution

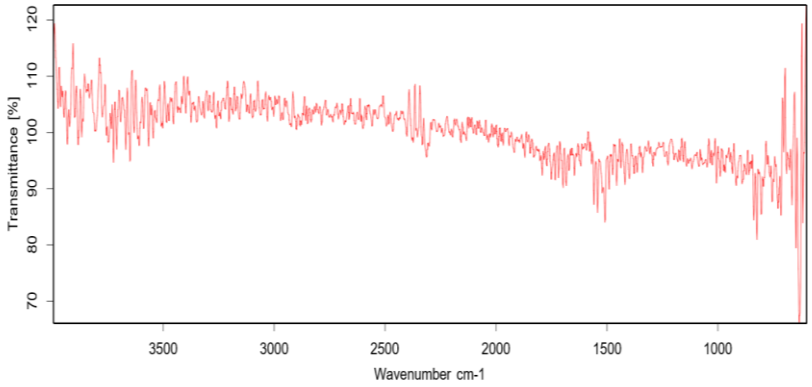
1. Pipette out 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, and 3.0 ml in stock solution 2nd in 10 ml of volumetric flask in different volumetric flask.
2. Make the volume of each volumetric flask with a phosphate buffer of 6.8 pH.
3. Measure the absorbance of each dilution at the wavelength of 276 nm.

Conc. (µg/ml)	Absorbance
5	0.164
10	0.158
15	0.239
20	0.303
25	0.402
30	0.483



Calibration curve of Aceclofenac

7. FTIR spectroscopy



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold	< Shoulder
3974.2942	1.042	0.098	7.8510	14.044950	0
3963.1944	1.045	0.055	2705.4124	6.827039	0
3955.5673	1.064	0.014	49.6268	1.746775	0
3947.6694	1.027	0.067	44.1649	8.769302	0
3932.5122	0.978	0.192	24.0058	32.053654	0
3922.1946	1.010	0.057	52.9860	5.475017	0
3899.4529	1.025	0.097	2502.9655	10.154810	0
3883.9794	0.978	0.183	15.8058	27.215551	0
3867.7052	0.991	0.090	10.2670	15.287464	0
3846.6970	1.071	0.026	3077.2296	3.083268	0
3832.9044	1.061	0.038	9.9879	6.221797	0

3.2.2 Acetaminophen

1. Appearance

- **Physical form of API:** It is in fine crystalline powdery texture.
- **Color:** White to off-white.
- **Texture:** Fine or Granular.
- **Odor:** No odor or Faint characteristic odor.
- **Purity:** High purity, often exceeding 99% or even higher.
- **Storage:** Stored at temperature 2-8^{o}C in an air-tight glass container protected from direct sunlight and moisture.

2. Solubility

- **Acetaminophen**

Acetaminophen is soluble in water and readily soluble in various organic solvents such as ethanol, methanol, acetone, chloroform, and dimethyl sulfoxide (DMSO).

3. Solid state character

- Acetaminophen typically forms crystalline structures.

4. Melting point determination

- The melting point of acetaminophen is 169-170°C.

5. Microscopy

Microscopy of Acetaminophen Api was performed under a compound microscope and solid crystal-like appearance was observed under the microscope.

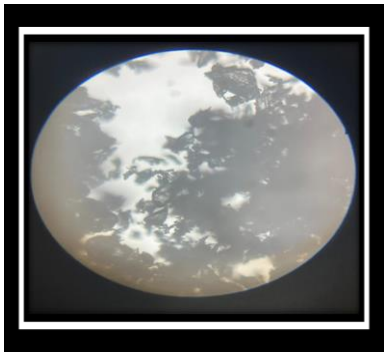


Fig. 5: Microscopy of Acetaminophen API.

6. UV spectroscopy

Preparation of stock and standard solution for calibration curve of Acetaminophen

A. Preparation of phosphate buffer 6.8 pH

Dissolve 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

B. Preparation of standard stock solution 1

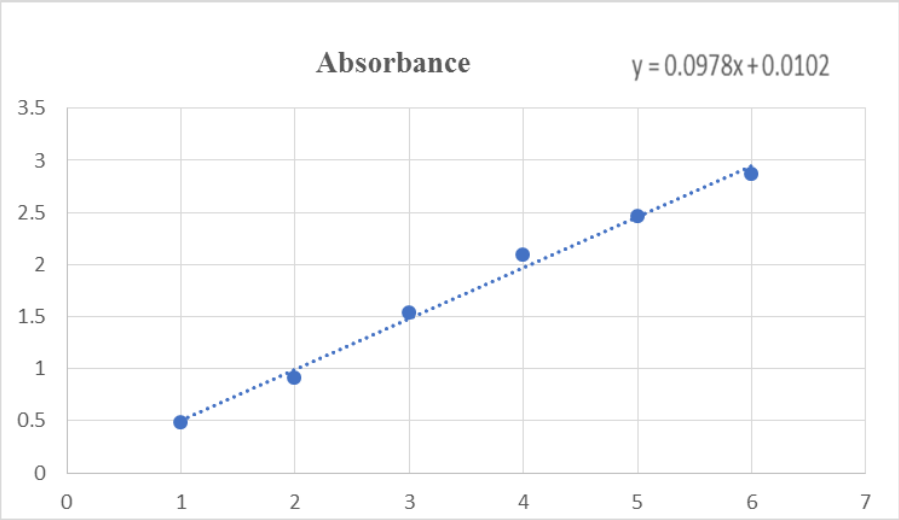
1. Weigh and transfer 0.10gm of acetaminophen in 100 ml of volumetric flask.
2. Add phosphate buffer 6.8 pH to make the volume up to 100ml in the volumetric flask.
3. Dissolve the drug in phosphate buffer. The concentration of that stock solution is 1000ug/ml.

C. Preparation of stock solution 2

1. Pipette out 10 ml of standard stock solution in 100 ml of volumetric flask.
2. Make the volume of 100 ml volumetric flask with phosphate buffer 6.8 pH.
3. The concentration of stock solution 2nd is 100ug/ml.

D. Dilution

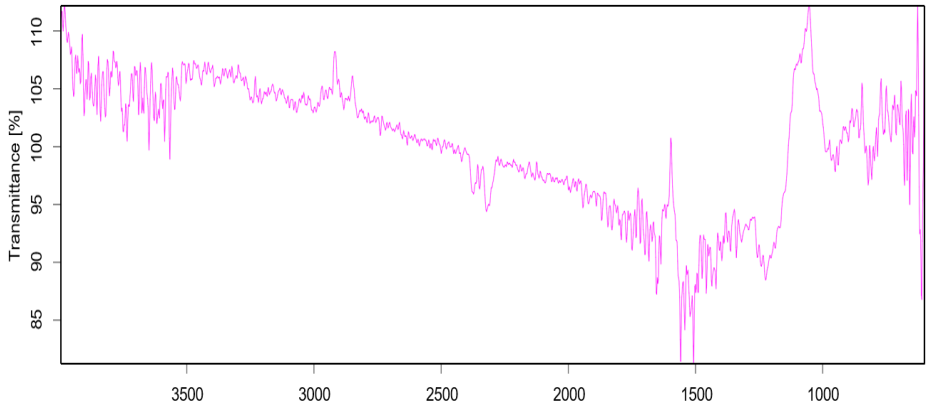
1. Pipette out 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, and 3.0 ml in stock solution 2nd in 10 ml of volumetric flask in different volumetric flask.
2. Make the volume of each volumetric flask with a phosphate buffer of 6.8 pH.
3. Measure the absorbance of each dilution at the wavelength of 257 nm.



Calibration curve of Acetaminophen

Conc (µg/ml)	Absorbance
5	0.481
10	0.907
15	1.531
20	2.092
25	2.456
30	2.862

7. FTIR spectroscopy



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold	< Shoulder
3986.4202	1.100	0.021	5.2437	6.155460	0
3970.0332	1.090	0.016	3546.4694	2.863753	0
3956.8186	1.079	0.011	3508.0381	2.231196	0
3944.6086	1.043	0.067	13.9487	17.764608	0
3932.5844	1.063	0.016	4.1756	5.021461	0
3924.4304	1.064	0.007	12.2161	1.018820	0
3917.7517	1.053	0.040	63.5229	8.453600	0
3903.5583	1.025	0.072	18.3017	17.154686	0
3891.9548	1.041	0.025	18.9043	5.470588	0
3881.0193	1.039	0.030	5.5526	7.923325	0
3866.6198	1.035	0.031	10.5564	8.841826	0

3.2.3. Procedure for drug layering

1.The layering of the drug was carried out using a Mini-Quest F Fluidized bed machine.
2. To operate the air flow regulator for controlling airflow. As per visual observation of the fluidized bed pattern adjust the air flow regulator.
3. Switch on the heating by setting the desired inlet temperature. Set the time for the desired time for the filter purging interval.
4. use the pressure control valve for the atomization air to adjust the desired automizing air pressure.
5. switch on the pump for the spray liquid and check the proper supply.
6. once the sprayed liquid has been sprayed out or granulation has been completed switch off the pump & close the atomization pressure control valve for the spray air.
7. Dry the product at optimum fluidization. Once the desired extract of drying has been reached. Switch off the heating.
8. leave the inlet process air pressure unchanged. Closed the pressure control valve for the process air (inlet airflow).

Process Operation

PARAMETERS	MIN	MAX	SET	ACT	UNIT
INLET TEMP (ºC)	20	44	40	33	Deg.c
PRODUCT TEMP	20	40	33	31	Deg.c
PROCESS TIME			90		Min

3.2.4 Preparation of coating solution

A. Aceclofenac primary layering

Weigh and transfer 10.35 gm of aceclofenac, 1 gm of hpmc, and 0.1 gm of the coloring agent in 50 ml of ethanol.

Sr.no	Ingredients	Percentage %	Function
1.	Aceclofenac	17.11	Analgesic
2.	Hpmc	0.16	Binder
3.	Coloring agent	0.01	Dye
4.	Ethanol	82.69	Solvent

- **Invitro dissolution study of Aceclofenac pellets**

Time (min)	Absorbance	Concentration (µg/ml)	Dilution factor	CDR	% CDR
5	1.313	92.01	920.1	829.0	255.1
10	1.397	98.14	981.4	883.2	271.7
15	1.408	98.94	989.4	890.4	273.9
30	1.808	128.14	1281	1153	354.8
60	1.975	140.33	1403	1262	388.6
120	1.477	103.98	1039	935.8	287.9
% Recovery	1.702	120.40	1204	1083	333.4

B. Ethylcellulose and Hpmc polymer layering

Weigh and transfer 2.64 gm of ethylcellulose, 0.10 gm of hpmc, and 0.06 gm of peg in 20 gm of methanol.

Sr.no	Ingredients	Percentage %	Function
1.	Ethylcellulose	11.57	Binder
2.	Hpmc	0.43	Binder
3.	Peg	0.26	lubricant
4.	Methanol	87.71	Solvent

- **Invitro dissolution of Ethylcellulose and Hpmc polymer pellets**

Time (min)	Absorbance	Concentration (µg/ml)	Dilution factor	CDR	% CDR
15	0.146	6.83	68.3	61.47	18.91
30	0.320	19.53	195.3	175.7	54.0
60	0.690	46.54	465.4	418.8	128.8
90	0.939	64.71	647.1	582.3	179.1
129	1.118	77.78	777.8	700.0	215.3
180	1.223	85.44	854.4	768.9	236.5
% Recovery	1.288	90.18	901.8	811.6	249.7

C. Acetaminophen secondary drug layering

Weigh and transfer 12.50 gm of Acetaminophen, 0.125 gm of hpmc, and 0.1 gm of the coloring agent in 50 ml of ethanol.

Sr.no	Ingredients	Percentage %	Function
1.	Acetaminophen	19.96	Antipyretic
2.	Hpmc	0.20	Binder
3.	Ethanol	79.84	Solvent

- **Invitro dissolution of Acetaminophen pllets**

Time (min)	Absorbance	Concentration (µg/ml)	Dilution factor	CDR	% CDR
5	6.923	78.53	785.3	706.7	706.7
10	6.937	78.69	786.9	708.2	708.2
15	7.133	80.92	809.2	728.2	728.2
30	7.364	83.54	835.4	751.8	751.8
60	7.613	86.37	863.7	777.3	777.3
% Recovery	7.782	88.27	882.7	784.4	784.4

4. CONCLUSION

Nowadays, there is a demand for dosage forms containing Circadian rhythms that have a significant role in medication release, leading to the development of personalized drug delivery systems that prioritize both therapeutic efficacy and patient compliance. New multiparticulate technologies with smart formulations are tailored to meet these demands. The lack of manufacturing repeatability and efficacy, as well as the high number of manufacturing variables owing to various formulation stages, restrict the number of marketed medicines in this category. With further technical innovation and improved design criteria, these challenges can be solved in the near future.

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