
Alarm
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# FORMULATION & CHARACTERIZATION OF NICORANDIL & BUDESONIDE LOADED DRUG DELIVERY USING DIFFUCAP TECHNOLOGY


**BY**
**MS. SOWJANYA BATTU,**
**Asst. Professor,**
**Dept. of Pharmaceutics,**
**CMR College of Pharmacy**

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# INTRODUCTION

## 1. MULTIPARTICULATE SYSTEMS[1]

**Multiparticulate systems are specifically suitable for achieving controlled or delayed release oral formulations with**

- **Smallest amount of risk of dose dumping.**
- **Flexibility of combination to achieve different release patterns.**
- **Less gastric residence time**

**Examples:**

**Pellets, Granules, Microparticles, Nanoparticles etc**

# ADVANTAGES OF MPDDS

1. Predictable, reproducible release with short gastric residence time.
2. Less intra and inter subject variability
3. Improved bioavailability
4. Reduced adverse effects and improved tolerability
5. Limited risk of local irritation
6. No risk of dosedumping
7. Ease of combinational therapy
8. Improved patient comfort and compliance.
9. Improved stability
10. Unique release patterns.

# 2. PELLETIZATION

- Pelletization is refered to as an agglomeration process, that converts fine powders or granules of bulk drugs into small, free flowing, spherical or semispherical units called as pellets.
- These are oral dosage forms consisting of multiplicity of small discrete units eachexibiting some desired characteristics.
- The size of pellets may range from mm to Micron or to Nano also.

# ADVANTAGES OF PELLETIZATION

1. Modified release dosage forms.
2. Reduces Inter and intra subject variability.
3. Produces spheroids with high loading capacity of API without producing large particles.
4. Have excellent flow and packing properties.
5. Can blend and deliver two or more chemically compatible or incompatible drugs into a single unit dosage form at the same time in GIT.
6. Incompatible drugs processed separately and mixed later with different release mechanisms to give a new modified release profile.

## 3. PULSATILE DRUG DELIVERY[2] & CONTROLLED RELEASE[3]

**Pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time period immediately after a predetermined off release period.**

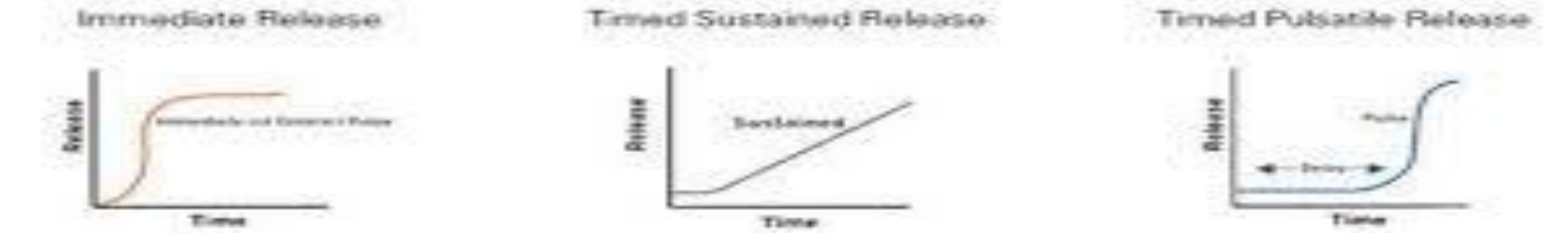
**It delivers the drug at Right place, at Right time and in Right amount and is basically a time controlled drug delivery system that controls the lag time independent of pH, enzymes and GI motility etc[4] .**

# NECESSITY FOR PULSATILE DRUG DELIVERY SYSTEMS[5]

1. Many body functions follow **circadian rhythm**, i.e., their activity increases or decreases with time.
2. Severity of diseases like bronchial asthma, myocardial infarction etc are also **time dependent.**
3. Drugs that produce **biological tolerance** and hence demand for a system that will prevent their continuous presence at the site of action as this tends to reduce their therapeutic effect.
4. **Protection from gastric environment** is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting.
5. To achieve localized action at distal organs of GIT and those that undergo extensive first-pass metabolism (ß-blockers).

# Table 1. Drugs used according to Chronological Behavior[5]

| Chronological behavior | Drugs used | Diseases |
|---|---|---|
| Acid secretion is high in the Afternoon and at night | H2 blockers | Peptic ulcer |
| Precipitation of attacks during night or at early morning | β2 agonist, Antihistamines | **Asthma** |
| BP is at its lowest during the sleep cycle and rises steeply during the early morning | Nitroglycerin, calcium channel blocker, ACE inhibitors | **Cardiovascular diseases** |
| Pain in the morning and more pain at night | NSAIDs, Glucocorticoids | Arthritis |
| Increase in the blood sugar level after meal | Sulfonylurea, Insulin | Diabetes mellitus |
| Cholesterol synthesis is generally higher during night than day time | HMG CoA reductase inhibitors | Hypercholesterolemia |

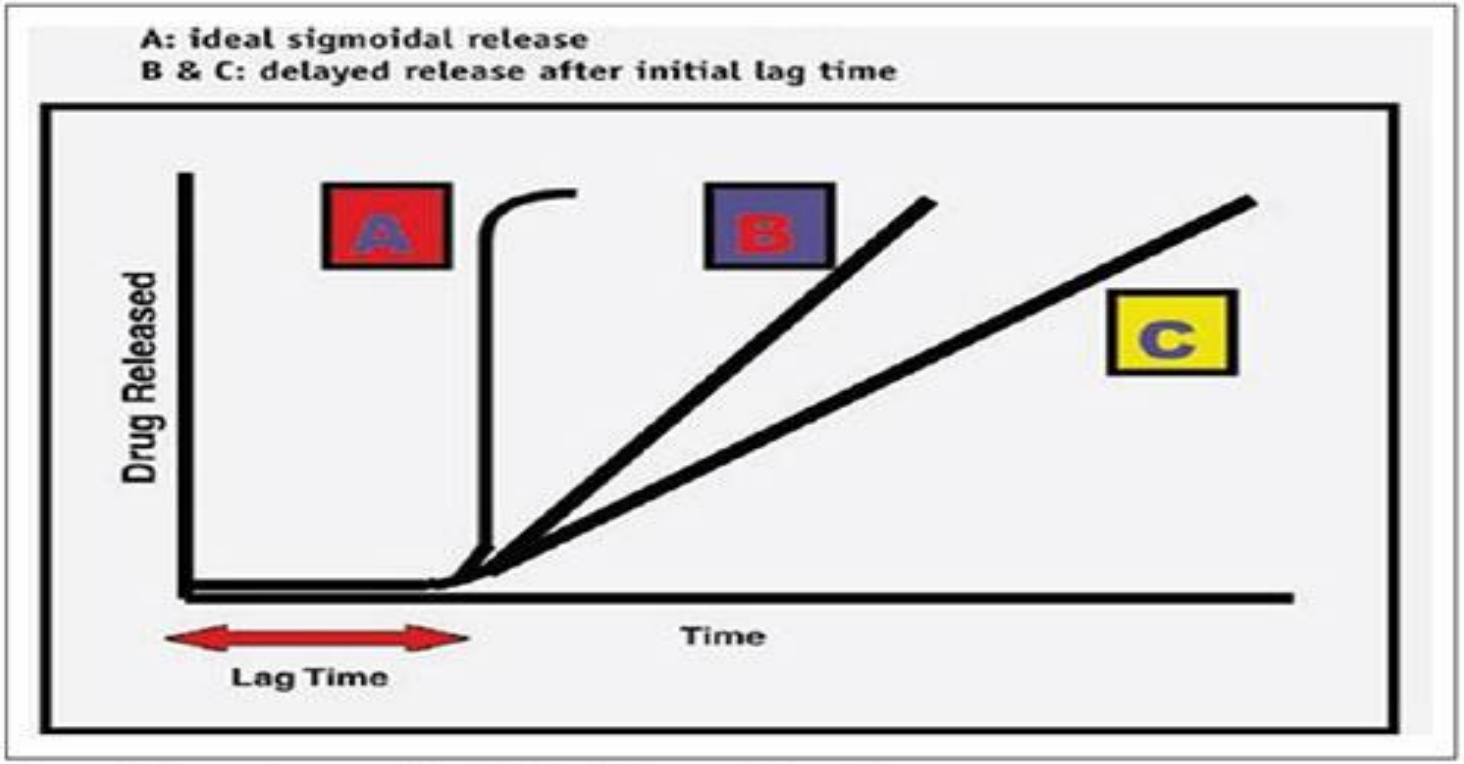




*Figure 1: Drug release profile of Pulsatile Drug Delivery System*

# AIM

Aim of the current study is to formulate, evaluate and perform *In-Vitro* drug release studies of multiparticulate-Pulsatile- Controlled drug delivery of combinatorial drugs like

**NICORANDIL:** Antihypertensive, Antianginal & Anti arrythmic.

**BUDENOSIDE:** Antiasthmatic, Treats colonic diseases

# OBJECTIVES

- To improve the bioavailability of poorly bioavailable drugs through oral route to treat chronic ailments.
- To develop a single dosage form of combinatorial drugs with different drug release patterns with both pulsatile and controlled delivery technologies.
- To produce reproducible and predictable drug release patterns.
- To reduce dose and dosing interval by developing once a day dosage regimen.
- To reduce dose dumping and side effects.
- To improve the patient compliance.

# 1. LITERATURE SURVEY

**ON DRUG DELIVERY SYSTEMS USED (DIFFUCAP TECHNOLOGY)**

1. A study on Development and evaluation of Multiparticulate colon targeted drug delivery system by combine approach of pH and bacteria by **Sanjay J.K Shirsagar et al., in 2011,** concluded that due to variations in GI transit times and microflora counts in different subjectsit is better to develop a system which will release the drug in colon based upon combined approach of pH and Bacteria.
2. A research paper on formulation and evaluation of salbutamol pellets prepared by Solution layering technique using various polymers conducted by **M.Chaudari Pallavi, et al., in 2014,** have shown that the proper selection of polymeric materials based on their physico chemical properties is important in designing pellets with suitable dissolution profile.
3. **Priese F & Wolf B in 2012,** worked to formulate inert microcrystalline cellulose pellets using batch laboratory Fluid bed apparatus with Wurster technique and reported that the coating process was stable and reproducible with 87-95% yields and also reported that the weight ratio of coating to core of 3:1 represents the best compromising proportion for high drug loading, sufficient yield and high drug recovery.

# Contn…

4. A work conducted on Indomethacin loaded multiparticulate pellets by **Kotta Kranthi Kumar and N. Dora Babu et al., in 2010,** have shown that 0.312 g of HPMC and 0.216 g of Ethyl Cellulose had shown 100 % drug release at 12$^{th}$ hour.
5. **Dharmaraj singh Chauhan and Shrenik Shah in 2012,** worked on pulsatile drug delivery system of Aceclofenac microspheres based on pulsincap technology using different plugging materials and their influence on lag phase. The study reported that out of sodium alginate, locust bean gum and psyllium husk which were used as plugging material, sodium alginate showed the satisfactory lag period.
6. **Mario Cazzola et al., (2011),** conducted a large population-based retrospective cross-sectional study for determining the extent of clinically recognized chronic obstructive pulmonary disease (COPD) and asthma, and the prevalence of associated cardiovascular diseases (CVDs). The study provides further evidence that patients with the diagnosis of COPD are at increased association with the diagnosis of most CVDs. It also documents that age clusters between 35 and 54 years are those at highest association of simultaneous presence of the diagnosis of CVD and that of COPD, with a progressive significant reduction in older age clusters.

# Contn…

7. **Carlos Iribarren,et al., (2004),** performed a cohort study among 70,047 men and 81 573 women, 18–85 years old, enrolled in a large managed care organization in Northern California. Because of the chronic, inflammatory nature of asthma, we hypothesized a possible link of asthma and prospective risk of coronary heart disease (CHD). They finally concluded that Asthma was independently associated with a modest but statistically significant increased hazard of CHD among women.
8. **Michela Bellocchia1,et al.,(2013),** evaluated that cardiovascular disease (CVD) is a common comorbidity in patients with chronic airway obstruction, and is associated with systemic inflammation and airway obstruction. The results of this study indicate that cardiovascular diseases are frequent in patients with chronic obstructive disorders, particularly in COPD patients. The strongest predictors of CVD are age and airway obstruction. COPD patients have higher prevalence of ischemic heart disease and pulmonary hypertension. In the elderly the prevalence of PO and VO in asthma and COPD patients is similar.
9. **Maxime Dougados, et al., (2013),** evaluated the prevalence of comorbidities and compared their management in RA patients from different countries worldwide. And they reported that among RA patients, there is a high prevalence of comorbidities and their risk factors.

# Contn…

10. **Janice A. Husted, et al., (2011),** determined whether the presence of psoriatic arthritis (PsA) is associated with greater comorbidity, in particular cardiovascular morbidity, compared to psoriasis without arthritis. And they reported the prevalence of hypertension, obesity, hyperlipidemia, type 2 diabetes mellitus, and at least 1 cardiovascular event in PsA patients was 37.1%, 30.0%, 20.7%, 12.0%, and 8.2%, respectively. This was significantly higher than in psoriasis without arthritis patients, with unadjusted ORs ranging from 1.54 to 2.59. The results suggest that inflammatory joint disease may play a role in both cardiovascular and noncardiovascular morbidity in PsA.

# PLAN OF WORK

1. LITERATURE COLLECTION
2. PREFORMULATION STUDIES
3. PROTOCOL OF WORK

**PHASE – I:** To formulate combinatorial drugs loaded multiparticulates (Pellets) using different controlled release and Pulsatile polymers with different ratios (Using DIFFUCAP TECHNOLOGY).

**PHASE – II:** To perform evaluation tests for the prepared pellets and draw the best polymer ratio for each drug.

**PHASE – III:** To formulate a single dosage form (Capsule) containing three dugs loaded pellets with different drug release patterns.

# SIGNIFICANCE & PURPOSE OF SELECTING COMBINATORIAL DRUGS

- Chronic obstructive pulmonary disease (COPD) and asthma are conditions associated with many comorbidities at the time of diagnosis. In particular, there is **solid evidence that patients with COPD are at increased risk of cardiovascular disease (CVD)**[6-9].
- In a study conducted by **Mario Cazzola et al., (2012),** determined the extent of clinically recognized COPD and asthma, and the prevalence of associated CVDs using information obtained from the Health Search Database (HSD) owned by the Societa` Italiana MediciGenerici (SIMG).
- **Carlos Iribarren (2004),** prooved that patients with asthma are at increased risk of coronary heart diseases.
- **Dougados M, et al (2013),** prooved the prevalence of risk factors for cardiovascular and cancer diseases in the 3920 patients with rheumatoid arthritis. IBD, inflammatory bowel disease.

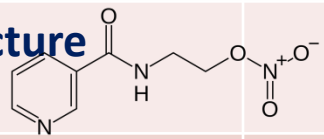
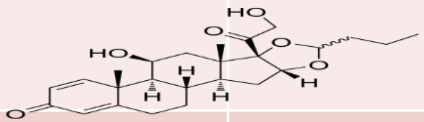
# Contn…

Thus from the above Literature it was proved that the comorbidity in patients is common for older age people above 40 years and out of all, the diseases such as **ASTHMA, CVD's, RHEUMATOID ARTHRITIS** are more prevalent in geriatrics along with the above mentioned ones, diseases associated with COLON (IBD's, Chron;s disease) are also common.

**Thus the drugs selected to treat the above mentioned comorbidities are:**

1. **NICORANDIL : For CVD's**
2. **BUDESONIDE : For ASTHMA & IBD's**

# DRUGS PROFILES

| PARAMETER | NICORANDIL | BUDESONIDE |
|---|---|---|
| **Formula** | $C_8H_9N_3O_4$ | $C_{25}H_{34}O_6$ |
| **Structure** |  |  |
| **Pharmacokinetic data:**<br>**Bioavailability**<br>**Protein Binding**<br>**Metabolism**<br>**Half Life**<br>**Excretion** | <br>65-70 %<br>25 %<br>Hepatic<br>1 Hour<br>21 % (Renal) | <br>10 – 20 %<br>85 – 90 %<br>Hepatic<br>2 – 3.6 hrs<br>Renal, Feacal |
| **Mechanism of Action** | Nicorandil activates K+ATP channel, causing K+ efflux. | Depresses the migration of polymorphonuclear leukocytes and fibroblasts. |
| **Therapeutic Uses** | vasodilatory drug used to treat angina. | used for the treatment of asthma, COPD & IBD's. |

# MATERIALS USED

| S.No. | MATERIALS | PURPOSE | PURCHASED FROM |
|---|---|---|---|
| 1 | BUDESONIDE | Active ingredient | Gift sample from Lee Pharma, Visakapatnam. |
| 2 | NICORANDIL | Active Ingredient | Gift sample from Lee Pharma, Visakapatnam. |
| 3. | SUGAR SPHERES | Core | Gift sample from Lee Pharma, Visakapatnam. |
| 3 | HPMC E55 ( HYPROMELLOSE) | CR Polymer | Gift sample from Lee Pharma, Visakapatnam. |
| 4 | ETHYL CELLULOSE 7,10,20 CPS | CR Polymer | CMR College of Pharmacy, Hyd. |
| 5 | EUDRAGIT s100, RL 100 | PR Polymer | Gift sample from Lee Pharma, Visakapatnam. |
| 6 | PVP k 30 | Binder | Pharma Tech Labs, Hyd. |
| 7 | ISO PROPYL ALCOHOL (IPA) | Vehicle | CMR College of Pharmacy, Hyd. |
| 8 | METHYLENE DICHLORIDE(MDC) | Vehicle | CMR College of Pharmacy, Hyd. |
| 9 | STARCH | Suspending vehicle | CMR College of Pharmacy, Hyd. |
| 10 | LACTOSE | Diluent | CMR College of Pharmacy, Hyd. |
| 11 | PURIFIED WATER | Vehicle | CMR College of Pharmacy, Hyd. |

# EQUIPMENT USED

| S.NO | EQUIPMENT | COMPANY |
|---|---|---|
| 1 | Fluidized bed processor | Platinum Pharma Tech / PPTFBC |
| 2 | Bulk electronic balance | LC/GC |
| 3 | Digital weighing balance | Sartorius |
| 4 | Sifter | Platinum Pharma Tech |
| 5 | Coating pan | Platinum Pharma Tech / PPTC |
| 6 | Dissolution apparatus | Lab India |
| 7 | UV Spectrophotometer | Lab India USP 2000 |
| 8 | Tap density Apparatus | Electro lab |
| 9 | Rapid dryer | Platinum Pharma Tech |

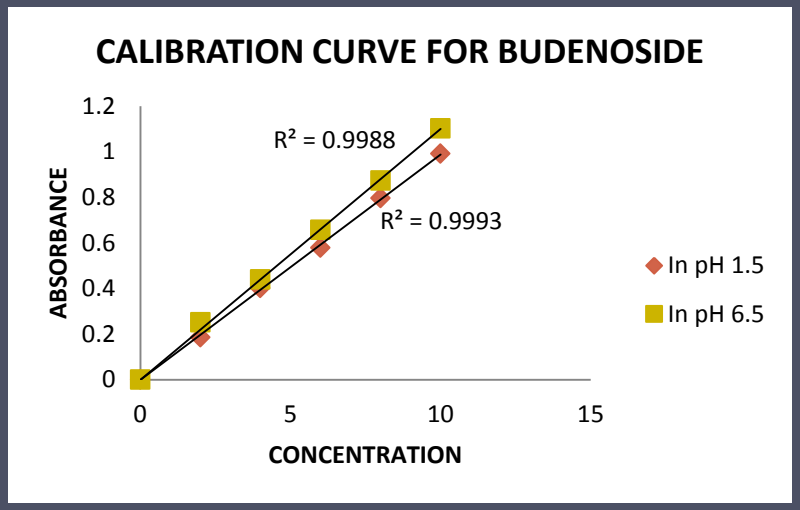
# 1. CALIBRATION CURVE VALUES

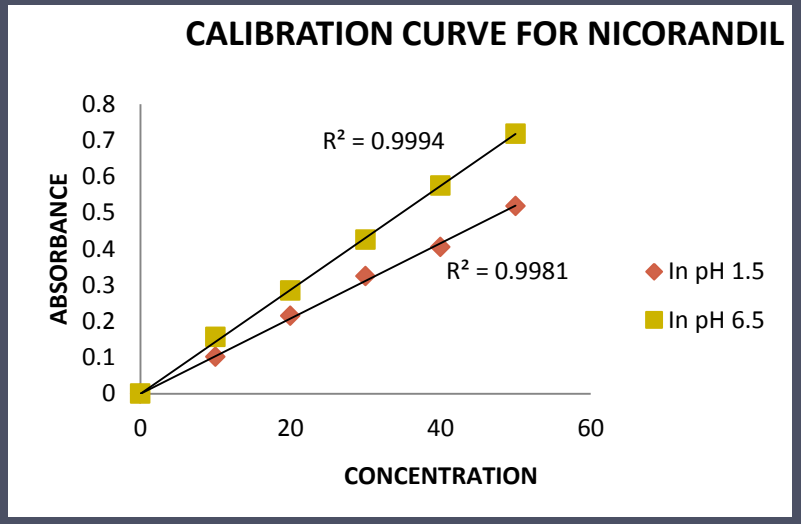
## FOR BUDESONIDE

| S.No | Concentration (mcg/ml) | Absorbance in 1.5 pH | Absorbance in 6.5 pH |
|---|---|---|---|
| 1 | 0 | 0 | 0 |
| 2 | 2 | 0.185 | 0.251 |
| 3 | 4 | 0.401 | 0.439 |
| 4 | 6 | 0.578 | 0.657 |
| 5 | 8 | 0.796 | 0.873 |
| 6 | 10 | 0.992 | 1.103 |

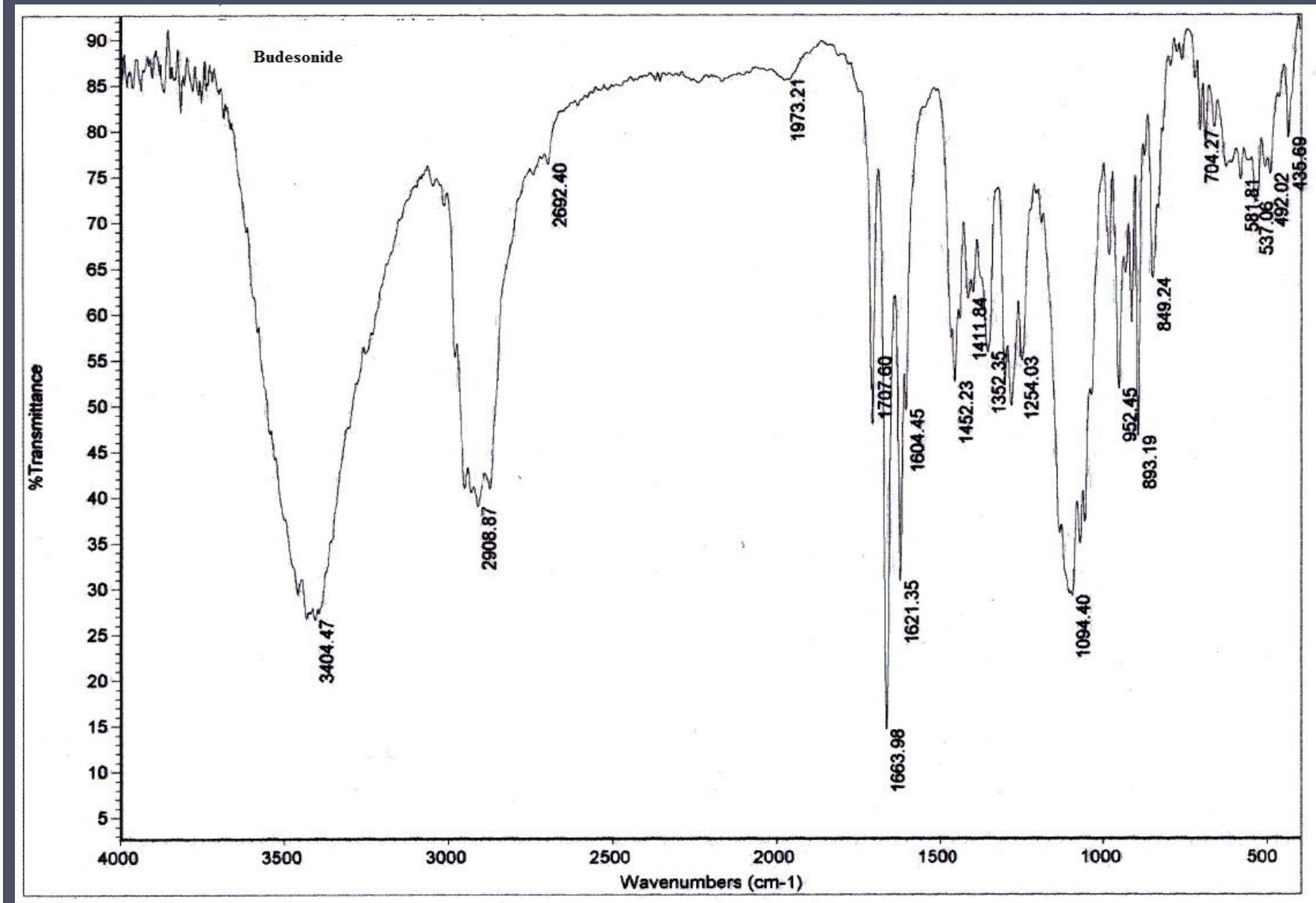
## FOR NICORANDIL

| S. No. | Concentration (µg/ml) | Absorbance in 1.5 pH | Absorbance in 6.5 pH |
|---|---|---|---|
| 1 | 0 | 0 | 0 |
| 2 | 10 | 0.102 | 0.202 |
| 3 | 20 | 0.215 | 0.315 |
| 4 | 30 | 0.325 | 0.425 |
| 5 | 40 | 0.405 | 0.505 |
| 6 | 50 | 0.518 | 0.618 |

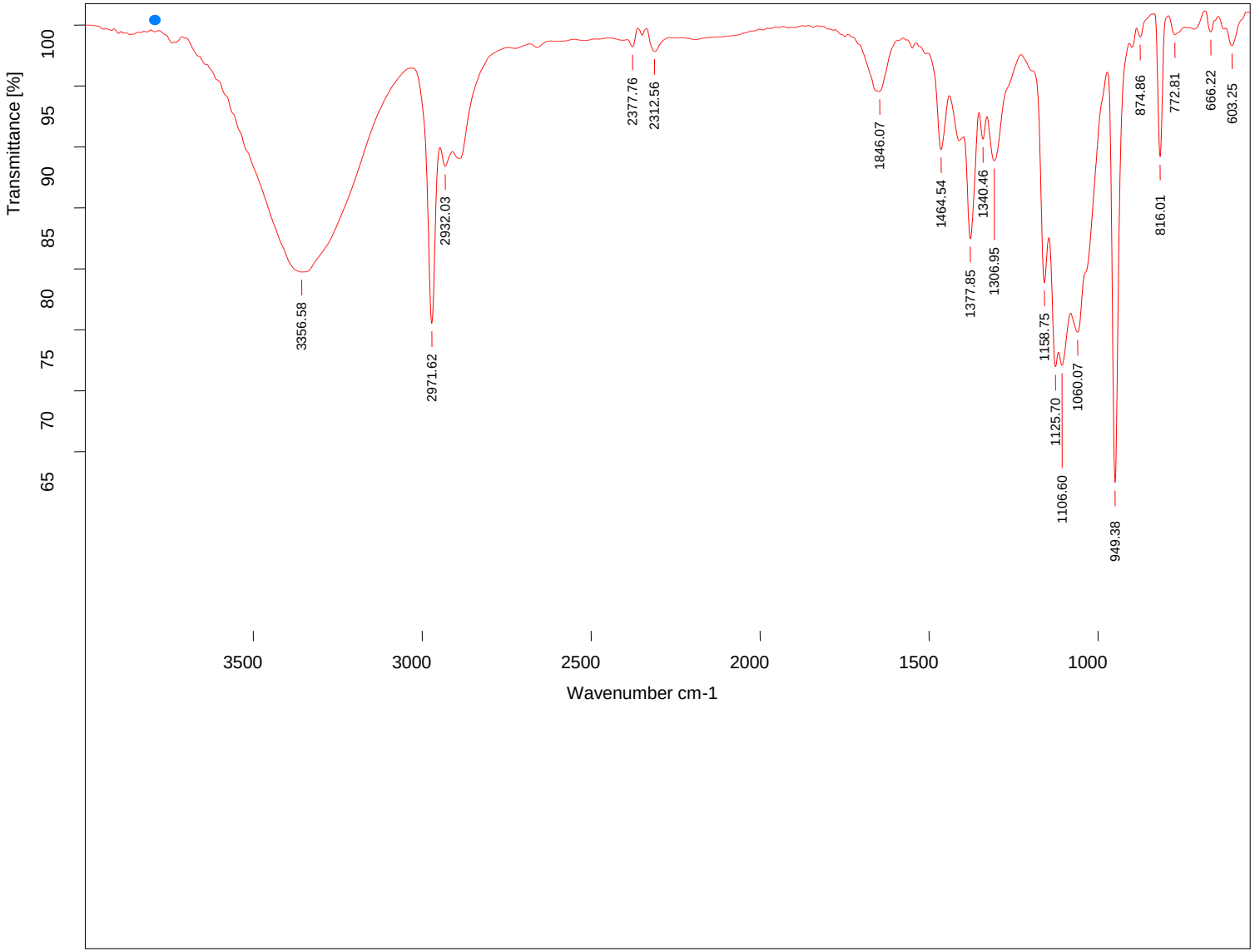


# FTIR REPORTS FOR BUDESONIDE



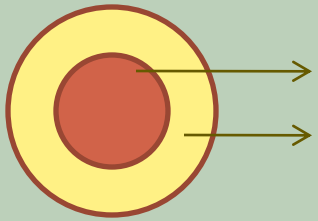
# FTIR REPORTS FOR NICORANDIL



# STEPS INVOLVED IN THE FORMULATION OF MULTIPARTICULATES WITH PULSATILE & CONTROLLED RELEASE POLYMERS

Includes 3 steps

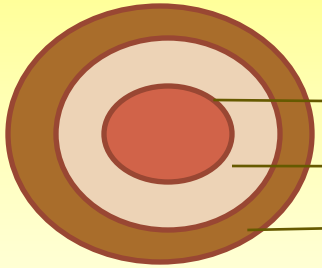
## STEP 1: COATING WITH DRUG ON NON-PARIEL SEEDS (Sugar Spheres)



Sugar Sphere (Non-Pareil seed)

Drug Layer on Sugar Sphere

## STEP2: COATING WITH CONTROLLED RELEASE POLYMER ON DRUG LOADED PELLETS.

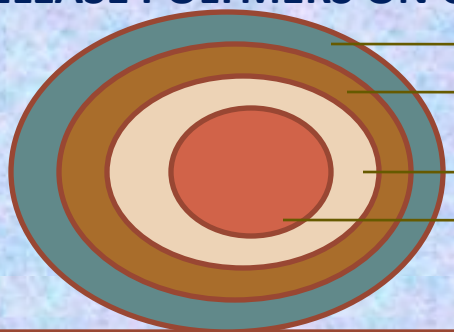


Sugar Sphere

Drug Layer

Control release coating layer

## STEP 3: COATING WITH PULSATILE RELEASE POLYMERS ON CONTROLLED RELEASE PELLETS

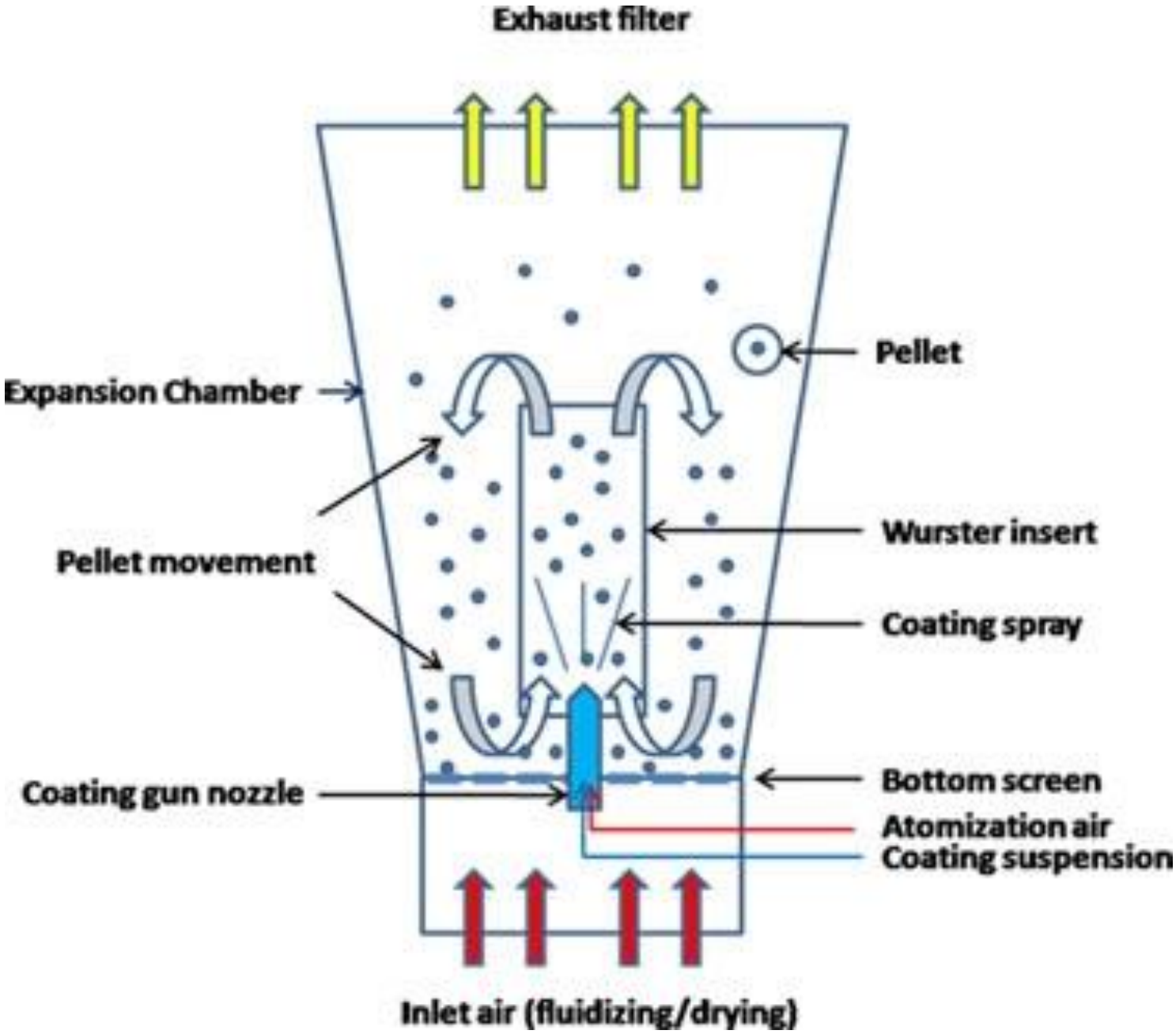


PR polymer Layer

CR Polymer Layer

Drug Layer

Sugar Sphere


Exhaust filter
Pellet
Expansion Chamber
Wurster insert
Pellet movement
Coating spray
Coating gun nozzle
Bottom screen
Atomization air
Coating suspension
Inlet air (fluidizing/drying)

# FORMULATION TABLE FOR STEP 1

## DRUG : NICORANDIL

| INGREDIENTS | Qty in gm |
|---|---|
| Nicorandil Hcl | 50 |
| Sugar spheres (25# - 30#) | 50 |
| SLS | 1.8 |
| Lactose | 6 |
| SSG | 3.6 |
| Mannitol | 9 |
| sucrose | 25 |
| PVP K-30 | 5 |
| IPA | 30 |
| **Total** | **150.4** |

## DRUG : BUDESONIDE

| INGREDIENTS | Qty in gm |
|---|---|
| Budesonide | 10 |
| Sugar spheres (25# - 30#) | 50 |
| Lactose Monohydrate | 24 |
| PVP K-30 | 5 |
| IPA | 30 |
| **Total** | **89** |

# FORMULATION TABLE FOR STEP 2

## DRUG : BUDESONIDE

| Polymer for CR | B1 | | B2 | | B3 | | B4 | | B5 | | B6 | | B7 | | B8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Drug loaded pellets (g)** | % | **89** | % | **89** | % | **89** | % | **89** | % | **89** | % | 89 | % | 89 | % | 89 |
| Ethyl cellulose 7 cps | 1 | 0.89 | 2 | 1.78 | | | | | | | | | | | | |
| Ethyl cellulose 10 cps | | | | | 1 | 0.89 | 2 | 1.78 | | | | | | | | |
| Ethyl cellulose 20 cps | | | | | | | | | **1** | **0.89** | **2** | **1.78** | | | | |
| HPMC HP55 | | | | | | | | | | | | | 1 | 0.89 | **2** | **1.78** |
| **Total** | | **89.89** | | **90.78** | | **89.89** | | **90.78** | | **89.89** | | **90.78** | | **89.89** | | **90.78** |

## DRUG : NICORANDIL

| Polymer for CR | N1 | | N2 | | N3 | | N4 | | N5 | | N6 | | N7 | | N8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Drug loaded pellets (g)** | % | **150.4** | % | **150.4** | % | **150.4** | % | **150.4** | % | **150.4** | % | 150.4 | % | 150.4 | % | 150.4 |
| Ethyl cellulose 7 cps | 1 | 1.504 | 2 | 3.008 | | | | | | | | | | | | |
| Ethyl cellulose 10 cps | | | | | 1 | 1.504 | 2 | 3.008 | | | | | | | | |
| Ethyl cellulose 20 cps | | | | | | | | | **1** | **1.504** | **2** | **3.008** | | | | |
| HPMC HP55 | | | | | | | | | | | | | 1 | 1.504 | 2 | 3.008 |
| **Total** | | **151.90** | | **153.408** | | **151.904** | | **153.408** | | **151.904** | | **153.408** | | **151.904** | | **153.408** |

# FORMULATION TABLE FOR STEP 3

## DRUG : BUDESONIDE

| Polymer For PR | MPP1 | | MPP2 | | MPP3 | | MPP4 | | MPP5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **CR Pellets** | % | **90.78** | % | **90.78** | % | **90.78** | % | 90.78 | % | 90.78 |
| Eudragit S 100 | 10 | 9.078 | | | 5 | 4.539 | 6 | 5.4468 | 4 | 3.6312 |
| Eudragit RL 100 | | | 10 | 9.078 | 5 | 4.539 | 4 | 3.6312 | 6 | 5.4468 |
| **Total** | | **99.858** | | **99.858** | | **99.858** | | **99.858** | | **99.858** |
| Assay | | 10.01 | | 10.01 | | 10.01 | | 10.01 | | 10.01 |
| Fill Wt for 10 mg Dose | | 100 | | 100 | | 100 | | 100 | | 100 |

## DRUG : NICORANDIL

| Polymer For PR | MPP1 | | MPP2 | | MPP3 | | MPP4 | | MPP5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **CR Pellets (g)** | % | **153.408** | % | **153.408** | % | **153.408** | % | 153.408 | % | 153.408 |
| Eudragit S 100 | 100 | 153.408 | | | 50 | 76.704 | 60 | 92.0448 | 40 | 61.3632 |
| Eudragit RL 100 | | | 100 | 153.408 | 50 | 76.704 | 40 | 61.3632 | 60 | 92.0448 |
| **Total** | | **306.816** | | **306.816** | | **306.816** | | **306.816** | | **306.816** |
| Assay | | 16.30 | | 16.30 | | 16.30 | | 16.30 | | 16.30 |
| Fill Wt for 20 mg Dose | | 122.72 | | 122.72 | | 122.72 | | 122.72 | | 122.72 |

## FINAL FILL WEIGHT OF OPTIMIZED DOSAGE FORM (CAPSULE)

| Final Dosage Form | Dose in mg | Fill Weight in mg |
|---|---|---|
| Nicorandil | 20 | 123 |
| Budesonide | 10 | 100 |
| Total | 30.00 | **223.00** |

## PROCESS PARAMETERS FOR PREPARING PELLETS USING FLUIDIZED BED PROCESSOR

| S. NO | Process Parameter | Range |
|---|---|---|
| 1 | Inlet temperature (°C) | 45-50 |
| 2 | Product temperature (°C) | 40-45 |
| 3 | Exhaust temperature(°C) | 30-45 |
| 4 | Atomization (barr) | 2-4.5 |
| 5 | Spray rate (g/min) | 60-120 |
| 6 | Wurster height (mm) | 20-50 |
| 7 | Pump RPM | 15-30 |

# STEP – 1 : DRUG LOADING

The calculated quantity of sugar spheres were taken into the conventional coating pan. After ensuring the integrity of the apparatus the operation was started by setting the temperature, spray pressure, spray rate etc.

Drug loading process was started by spraying the binder solution first till complete wetting of spheres is ensured (20 mns) then the API and excipient blend is added over the periel seeds and processed for 25 mns until uniform layering takes place and are subjected for drying.

The dried pellets were passed through the sieves 14# and 18#. The ups and downs of each sieve were collected separately. Pellets retained on 18# are used for STEP 2.

# STEP – 2 : CR RELEASE LAYERING

Purified water was taken and kept for heating until it reached 60°C- 70°C and EC was added under continuous stirring for 30minutes (or) till clear solution was formed.

In an other beaker MDC and IPA were taken and mixed thoroughly, the prepared polymer dispersion was poured into it with constant stirring.

Drug loaded pellets were loaded into FBP and the pellets were warmed till the product temperature of 40±2°C was obtained.

The sub coating dispersion prepared was sprayed with following parameters. The dispersion was kept under continuous stirring during the coating process.

The coating was continued till target weight build up was obtained &dried at the product temperature of 33°C–35°C for 10 minutes. The dried pellets were passed through the sieves 14# and 20#. The ups and downs of each sieve were collected separately. Pellets retained on 20# are used for STEP 3.

# STEP – 3 : PR RELEASE LAYERING

Purified water was taken and kept for heating until it reached 60°C- 70°C and Eudragit was added under continuous stirring for 30minutes (or) till clear solution was formed.

In an other beaker Acetone and Ethyl alcohol were taken and mixed thoroughly, the prepared polymer dispersion was poured into it with constant stirring.

Drug loaded pellets were loaded into FBP and the pellets were warmed till the product temperature of 40±2°C was obtained.

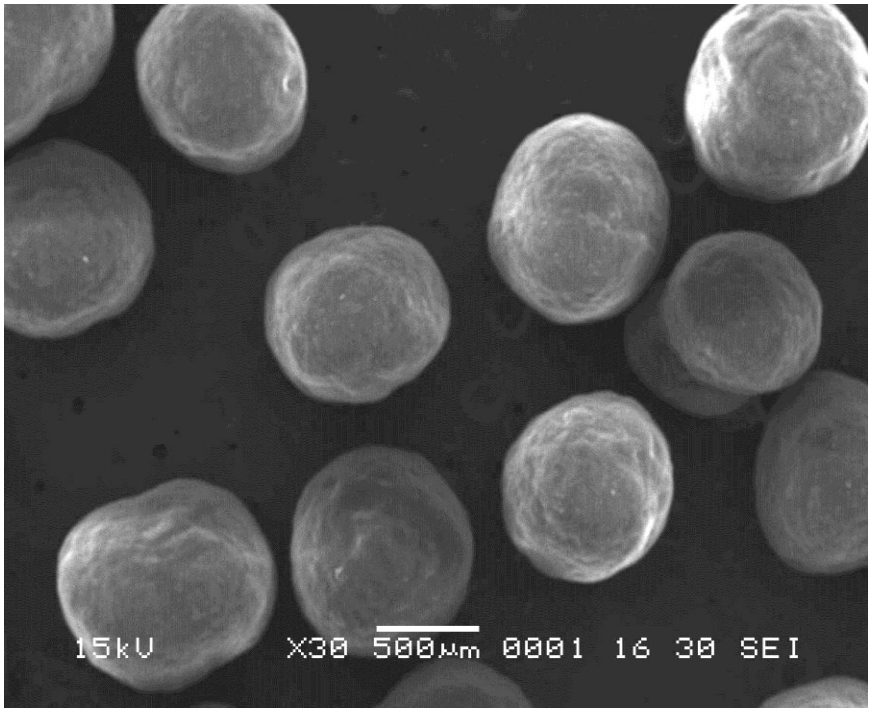
The sub coating dispersion prepared was sprayed with following parameters. The dispersion was kept under continuous stirring during the coating process.

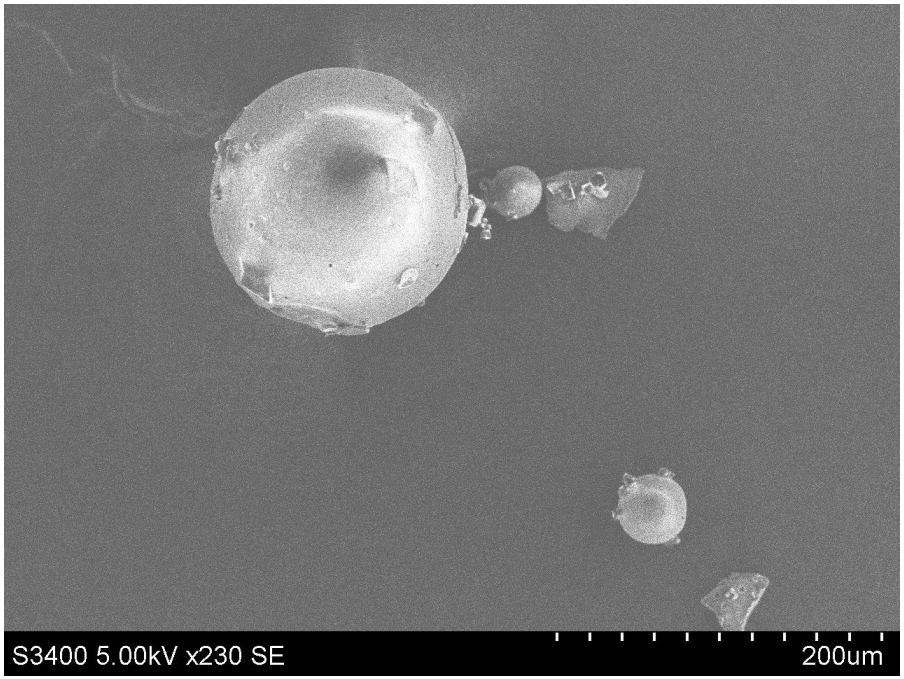
The coating was continued till target weight build up was obtained. The fluidization air flow was reduced to suitable level and the sub coated pellets were dried at the product temperature of 33°C–35°C for 10 minutes.

# CHARACTERIZATION OF PELLETS

1. Characterization studies for prepared pellets.
2. Optimizing the best formula for each drug, based on *In-Vitro* drug release studies.
3. Performing FTIR studies for optimized formulation.
4. Formulating the optimized formula into dosage form.
5. Characterization studies for final dosage form.

# SEM Analysis Reports for BUDOSONIDE & NICORANDIL PEİLETS

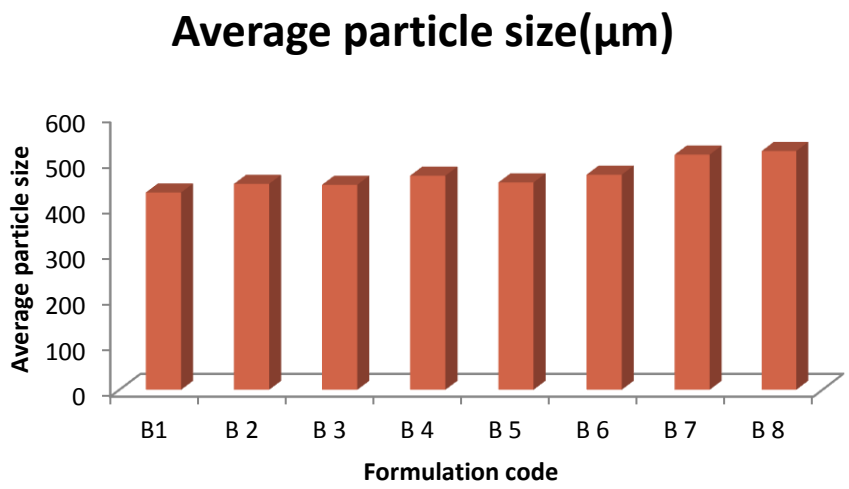


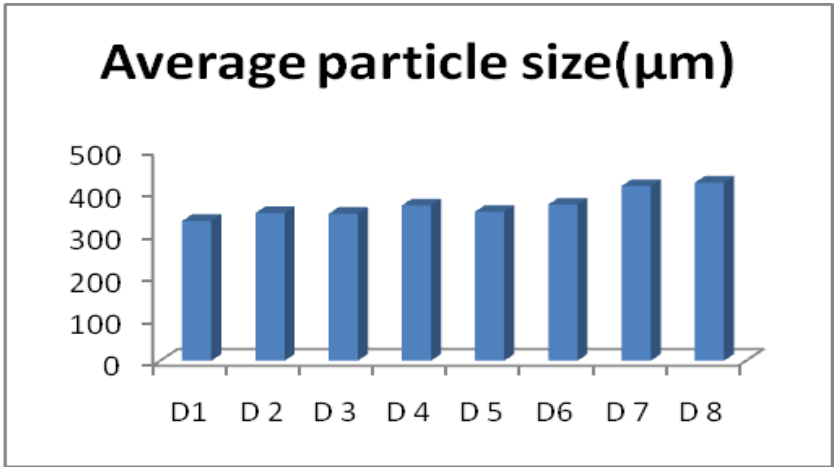



# Average Particle Size analysis for BUDOSONIDE formulations B1-B8 & NICORANDIL formulations N1 – N8 with Graphical representation

| Formulation code | Average particle size(µm) |
|---|---|
| **B1** | 432 |
| **B 2** | 451 |
| **B 3** | 449 |
| **B 4** | 469 |
| **B 5** | 454 |
| **B 6** | 471 |
| **B 7** | 515 |
| **B 8** | 523 |

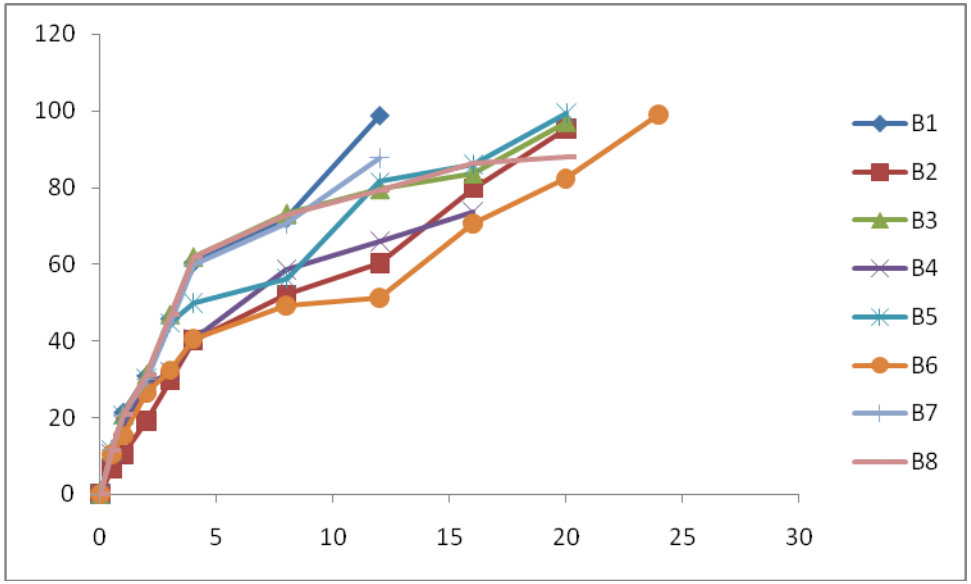
| Formulation code | Average particle size(µm) |
|---|---|
| B1 | 332 |
| B 2 | 351 |
| B 3 | 349 |
| B 4 | 369 |
| B 5 | 354 |
| B 6 | 371 |
| B 7 | 415 |
| B 8 | 423 |



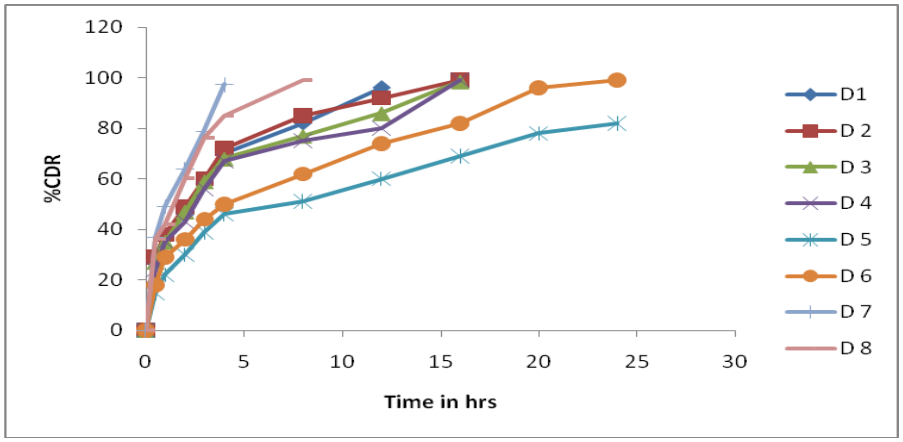
# In-Vitro drug release data of Budesonide CR pellets

| TIME (h) | Cumulative Percent Of Drug Released | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.25 | 10.5 | 6.7 | 11.5 | 10.4 | 11.5 | 10.5 | 11.5 | 11.5 |
| 0.5 | 21.3 | 10.3 | 20.8 | 18.1 | 20.6 | 15.3 | 20.6 | 20.8 |
| 1 | 30.8 | 19.1 | 31.2 | 28.6 | 30.1 | 26.4 | 30.1 | 31.2 |
| 2 | 45.7 | 29.8 | 46.8 | 31.8 | 44.7 | 32.4 | 44.7 | 46.8 |
| 3 | 60.4 | 40.1 | 61.8 | 40.6 | 49.8 | 40.6 | 59.8 | 61.8 |
| 4 | 71.8 | 52.1 | 73.1 | 58.6 | 56.3 | 49.2 | 70.4 | 73.1 |
| 6 | 98.7 | 60.3 | 79.4 | 65.8 | 81.5 | 51.3 | 87.6 | 79.4 |
| 8 | -- | 79.8 | 83.5 | 73.6 | 86.0 | 70.7 | -- | 86.2 |
| 10 | -- | 95.4 | 96.9 | 95.9 | 99.4 | 82.4 | -- | 88.0 |
| 12 | -- | -- | -- | -- | -- | 99.1 | -- | -- |



# In-Vitro % Cumulative drug release data of Nicorandil CR pellets

| Time (hrs) | N1 | N 2 | N 3 | N4 | N 5 | N 6 | N 7 | N 8 |
|---|---|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | **0** | 0 | 0 |
| **025** | 28 | 29 | 27 | 24 | 15 | **18** | 37 | 36 |
| **0.5** | 37 | 38 | 35 | 35 | 22 | **29** | 49 | 42 |
| **1** | 46 | 49 | 47 | 43 | 30 | **36** | 64 | 60 |
| **2** | 58 | 60 | 59 | 56 | 39 | **44** | 79 | 76 |
| **3** | 70 | 72 | 68 | 67 | 46 | **50** | 97.4 | 85 |
| **4** | 82 | 85 | 77 | 75 | 51 | **62** | | 99 |
| **6** | 96 | 92 | 86 | 80 | 60 | **74** | | |
| **8** | - | 99.2 | 98.6 | 99 | 69 | **82** | | |
| **10** | - | -- | -- | -- | 78 | **96** | | |
| 12 | | | | | 82 | **99.2** | | |

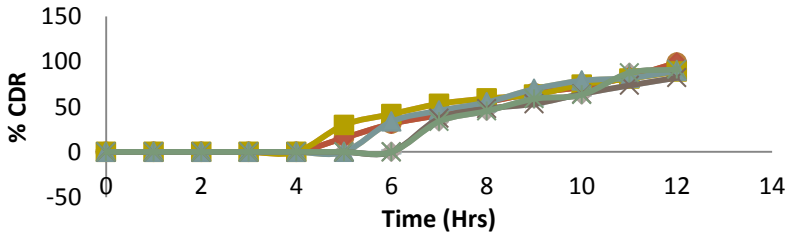


# In-Vitro % Cumulative drug release data of Budosonide & Nicorandil Multiparticulate Pulsatile pellets

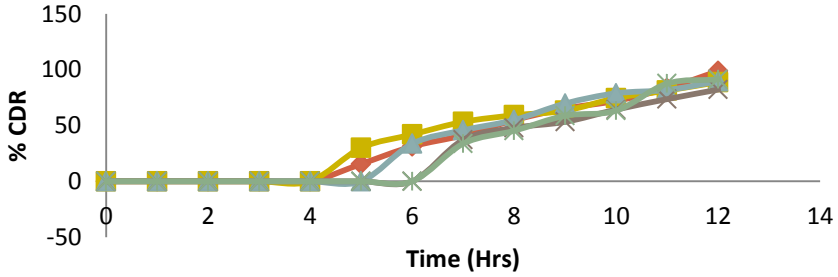
| Time (Hr) | BP1 | BP2 | BP3 | BP4 | BP5 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 |
| 5 | 17.8 | 28.0 | 0 | 0 | 0 |
| 6 | 21.67 | 34.8 | 32.8 | 0 | 0 |
| 7 | 32.457 | 47.057 | 41.247 | 39.218 | 32.104 |
| 8 | 48.901 | 55.928 | 57.842 | 42.156 | 45.247 |
| 9 | 51.020 | 65.185 | 63.217 | 54.781 | 63.217 |
| 10 | 69.782 | 74.057 | 70.198 | 66.547 | 74.210 |
| 11 | 83.218 | 81.257 | 81.784 | 73.574 | 87.487 |
| 12 | 98.740 | 88.814 | 89.457 | 82.107 | 91.240 |

| Time (Hr) | NP1 | NP2 | NP3 | NP4 | NP5 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 |
| 5 | 15.5 | 29.9 | 0 | 0 | 0 |
| 6 | 31.2 | 41.9 | 33.6 | 0 | 0 |
| 7 | 41.147 | 53.210 | 45.687 | 37.045 | 33.668 |
| 8 | 54.740 | 59.108 | 54.879 | 47.849 | 45.217 |
| 9 | 65.180 | 63.218 | 69.631 | 53.208 | 58.741 |
| 10 | 72.014 | 74.521 | 78.841 | 64.217 | 63.247 |
| 11 | 83.218 | 81.257 | 81.784 | 73.574 | 87.487 |
| 12 | 98.740 | 88.814 | 89.457 | 82.107 | 91.240 |

## In-Vitro drug release for Budosonide MP Pellets from B1 - B5




## In-Vitro drug release for Nicorandil MP Pellets from N1 - N5



# In-Vitro drug releaseKinetics for Budosonide & Nicorandil Multiparticulate Pulsatile pellets

| NICORANDIL | ZERO | FIRST | HIGUCHI | PEPPAS |
|---|---|---|---|---|
| | % CDR Vs T | Log % Remain Vs T | %CDR Vs √T | Log C Vs Log T |
| Slope | 3.5594989 | 0.04221913 | 19.9518931 | 0.77067530 |
| Intercept | 24.369577 | 1.91462548 | 5.87853744 | 1.12097599 |
| Correlation | 0.9434014 | -0.98614282 | 0.99127835 | 0.64682634 |
| R 2 | 0.8900062 | 0.97247767 | 0.98263278 | 0.41838431 |

| BUDESONIDE | ZERO | FIRST | HIGUCHI | PEPPAS |
|---|---|---|---|---|
| | % CDR Vs T | Log % Remain Vs T | %CDR Vs √T | Log C Vs Log T |
| Slope | 8.2744884 | 0.1404635 | 31.439431 | 1.3723862 |
| Intercept | 9.6436061 | 2.2014992 | 12.270997 | 0.7039675 |
| Correlation | 0.9501605 | 0.9248705 | 0.9665547 | 0.8767165 |
| R 2 | 0.9028049 | 0.8553855 | 0.9342281 | 0.7686318 |

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Thank
you