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A STUDY ON THE INITIAL AND DEVELOPED FORMULATIONS OF SALBUTAMOL SULPHATE TABLETS

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ABSTRACT

Extended release dosage forms are designed to achieve or prolong therapeutic effects by continuously releasing medication over an extended period after administration of a single dose. These systems are attractive because they can increase the bioavailability of the drug product, reduce the frequency of administration, maintain effective blood levels for a longer duration, minimize fluctuations between peak and trough concentrations, decrease side effects, and may improve the specific distribution of the drug.

INTRODUCTION

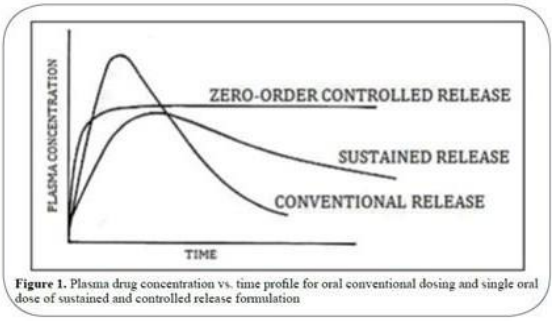


Figure 1. Plasma drug concentration vs. time profile for oral conventional dosing and single oral dose of sustained and controlled release formulation

Fig.1.1 Plasma drug concentration vs time profile.

Advantages of Sustain Release Dosage Forms

1. A decrease in intake frequency
2. Lessen adverse consequences
3. Consistent medication release over time.
4. Increased patient adherence.
5. Reduction of systemic and local side effects.

6. Increased utilization of drugs.
7. Enhanced therapeutic effectiveness.
8. Optimised treatment.

Disadvantages of Sustained Release Drug Delivery –

1. Excessive formulation costs.
2. Dosedumping-related toxicity.
3. The in vitro-in vivo relationship is frequently unpredictable and poor.
4. The potential for hazardous or adverse effects from the quick release of the medicine from its container (mechanical failure, mastication, or alcohol consumption).
5. Greater chance of clearing the first pass.

Extrusion and Spheronization technique - Extrusion–spheronization is considered one of the most effective techniques for delivering multiple potent drugs that exhibit high systemic toxicity. Owing to its benefits—such as high drug-loading capacity, uniform particle size distribution, and cost-efficiency—it offers significant potential in pharmaceutical applications. Additionally, these systems enable targeted drug delivery when coated appropriately, thereby enhancing the bioavailability of various medications.

The present review concentrates on the extrusion–spheronization technique, along with the influence of processing parameters (including extruder design, screen pressure, screw speed, temperature, moisture level, and spheronization conditions like load, speed, and duration) and formulation factors (such as excipients and active pharmaceutical ingredients) on the quality of the resulting pellets. Pellet quality is assessed using several evaluation methods that consider parameters like particle size distribution, morphology, friability, mechanical strength, density, porosity, flow behavior, and surface texture.

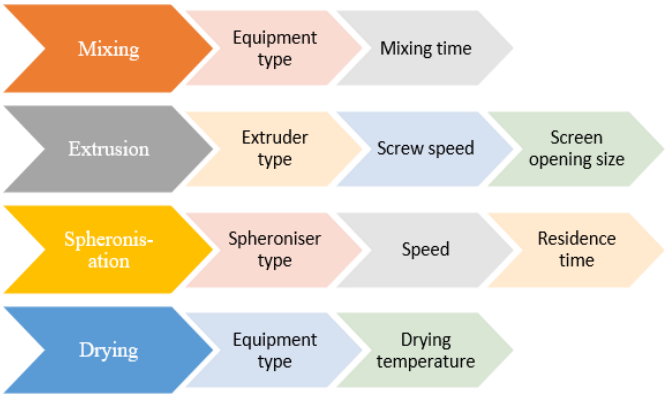
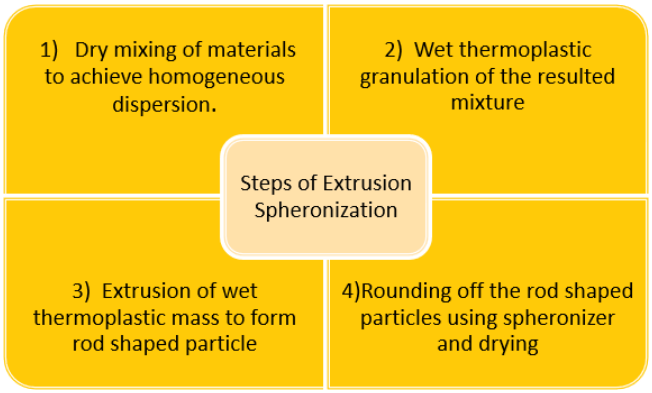
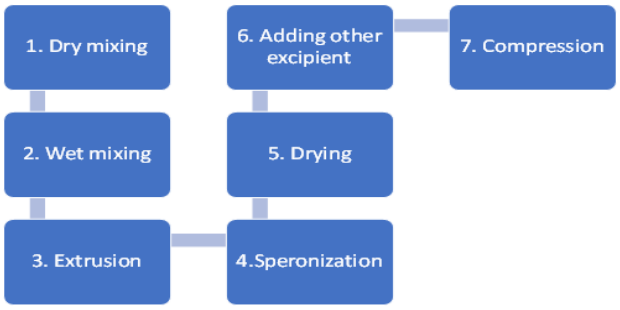


Fig.1.2. Processing flow chart indicating individual process variables.





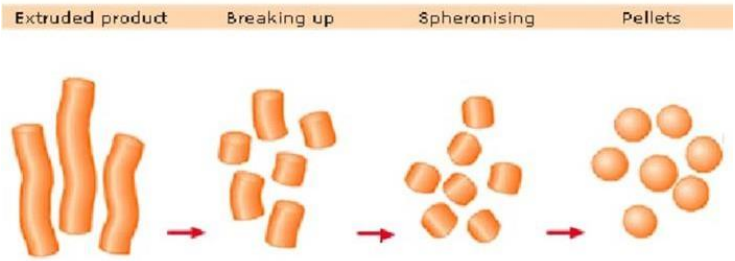
• Steps involved in formulation process

Formulation Procedure - Wet granulation serves as an important procedure in the formulation of prolonged-release matrix tablets. This method is frequently employed to produce pressed tablets. The granules obtained are more likely to satisfy the necessary physical requirements, as the process essentially consists of particle enlargement through various phases and the addition of a cohesive agent referred to as a binder.

Procedure -

 Formulating a damp mass by measuring, pulverizing, and mixing APIs with powder excipients, with water serving as the solvent.

- Conveying the wet mixture via a cold melt extruder to modify its physical characteristics.
- Sieving the extruded product to obtain spheroidal pellets or granules.



1. Dry obtained granules with the help of hot air oven the temperature 60^0c for 20 minutes.
2. After cooling pass this powder from the sieve using 6 to 12 mesh screens.
3. Mixing of the dried granules with the diluent such as microcrystalline cellulose, lubricant such as magnesium stearate and talc.
4. Compression of granules into tablets by using tablet compression machine.

Sr. No.	Author	Tittle	Relevance to Present Work
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2.	Ballard, B. E.,: Edited by J. R. Robinson. New York, Marcel Dekker (1978).	An overview of prolonged action drug dosage forms	Sustained & controlled Release drug delivery systems.
3.	Brazel JG, Peck GH,PeppasYT., using neural formulations. J		Pharmaceutical granulation and tablet
	Control Release,2000;26(2):211-215.		Formulation network in sustained release.
4.	J. E. Hogan, Drug Dev. Ind. Pharm.15(6,7),975-999(1989).		Information of HPMC
5.	Sinha VR, Agrawal MK, Agarwal A, Singh G, Ghai D. Critical Reviewsin Therapeutic Drug Carrier Systems. Begell House Inc.; (2009)	Extrusion – spheronization : Process variables and characterization.	Study of process variables.

Objective of The Study –

1. Salbutamol is used to treat the breathlessness, coughing, and wheezing that are signs of asthma and chronic obstructive pulmonary disease (COPD).

   → Salbutamol is prescribed to relieve shortness of breath, cough, and wheezing associated with asthma and COPD.

3. Sustained release dosage forms for salbutamol sulphate are designed to release a medication at a set pace while keeping the drug level stable for a particular period of time.

   → Sustained-release formulations of salbutamol sulphate are developed to deliver the drug gradually at a controlled rate, maintaining consistent drug levels over a defined duration.

4. The see-saw fluctuation in medication plasma levels is reduced by sustained release formulations.

   → Sustained-release dosage forms minimize the sharp rises and falls in drug concentration within the bloodstream.

5. The convenience of use and compliance of the patient are improved due to less frequent drug delivery.

   → Reduced dosing frequency enhances patient convenience and improves adherence to the treatment regimen.

Formulation strategy for oral SRDDS:

1. Diffusion Sustained System
2. Dissolution Sustained System
3. Methods using ion exchange
4. Methods using osmotic pressure
5. pH independent formulation Altered density formulation.

Plan of Work -

1. Literature based study:
2. Study need and objective:
3. Selection and Procurement of ingredients:
4. Equipment/instrument and method selection:
5. **Preformulation:**

- Preformulation evaluation study:
- Compatibility study of drug and excipient.
- λ max estimation (UV-VIS method)
- Optimisation and formulation development:
- Preliminary study and trial batches
- Development of formulation protocol.

6. Formulationsteps:

1) Extrution
2) Speronization
3) Drying
4) Adding other excipient
5) Compression

7. Evaluation:

- Hardnesstest
- Weightvariationstest
- Dissolution test
- Disintegrantiontest
- Friability test

Drug And Excipient Information:

Salbutamol Sulphate -

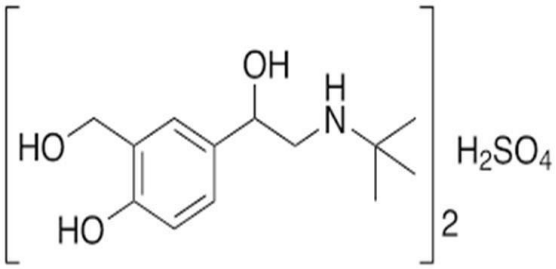


Fig.no.5.1 Salbutamol sulphate chemical structure.

Asthma and COPD are both managed using salbutamol, a short-acting and selective $beta_2$-adrenergic receptor agonist. It demonstrates greater selectivity for pulmonary $beta_2$ receptors than for $beta_1$ receptors in the heart, being approximately 29 times more selective for $beta_2$ receptors. Salbutamol is produced as a racemic mixture containing both R- and S-enantiomers. The R-isomer has about 150 times higher affinity for $beta_2$ receptors, whereas the S-isomer has been associated with adverse effects. This led to the development of levalbuterol, which consists solely of the R-isomer. Although levalbuterol is an enantiomerically pure form of salbutamol, its higher cost limits its widespread use. Salbutamol is commonly prescribed for the relief of acute bronchospasm in conditions such as bronchial asthma, chronic bronchitis, and other chronic respiratory diseases like COPD. It is also used to prevent exercise-induced asthma.

Hydroxyl propyl methyl Cellulose (HPMC) - The superior binder HPC demonstrates excellent compressibility and comparable binding effectiveness whether it is incorporated as a solution or in dry powder form. Hydroxypropyl methylcellulose (HPMC), a water-soluble cellulose-derived polymer, is widely used as a key binder in pharmaceutical applications. HPMC polymers are considered versatile binding agents because they perform effectively with both soluble and insoluble drugs, as well as across high and low dosage levels.

Lactose - In this formulation, lactose serves as the diluent. It is commonly used as a filler or diluting agent in tablets and capsules, except in lyophilized products and infant formulations. Lactose is also utilized as a carrier in dry powder inhalation systems. Based on crystallization and drying conditions, lactose can exist in different isomeric forms, such as lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. The three stable crystalline forms of lactose include α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous. Lactose appears as a white to off-white crystalline powder or particles. It is odorless and has a slightly sweet taste; α-lactose is approximately 20% sweeter than sucrose, while β-lactose is about 40% sweeter.

Magnesium Stearate - In this formulation, magnesium stearate functions as the lubricant. It has the molecular formula $C_{36}H_{70}MgO_4$ and a molecular weight of 591.34. Magnesium stearate consists of magnesium combined with a mixture of solid organic acids, mainly magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$), present in varying proportions. As defined in the Ph. Eur. (2005), it is a mixture of magnesium salts of different fatty acids, predominantly stearic acid and palmitic acid, along with small amounts of other fatty acids. It appears as a very fine, light, white powder that is either precipitated or milled, possessing low bulk density, a faint stearic acid-like odor, and a characteristic taste. When handled, it feels greasy and readily adheres to the skin.

Talc - In this formulation, talc is used as a glidant. Talc is a pure, hydrated magnesium silicate with a chemical formula approximating $Mg_6(Si_2O_5)_4(OH)_4$, and it may contain trace amounts of iron and aluminum silicates. It appears as a very fine, crystalline, odorless, soft, and smooth powder that ranges from white to grayish-white in color. The powder feels silky to the touch, readily adheres to the skin, and is non-gritty. Due to its stability, talc can be sterilized by heating at 160°C for at least one hour. It should be stored in a well-closed container in a cool, dry place.

Micro crystalline Cellulose (MCC) - In this formulation, microcrystalline cellulose (MCC) is used as a disintegrant. The official nonproprietary name for polyethylene oxide, as listed in the USP–NF, is polyethylene oxide, and it is also known by synonyms such as Polyox, Polyoxiante, and polyoxyethylene. Polyethylene oxide is a chemical compound defined in the USP–NF as a nonionic homopolymer of ethylene oxide, represented by a general formula in which *n* denotes the average number of oxyethylene units. It may also contain a suitable antioxidant or up to 3% silicon dioxide as an additive.

Materials And Instuments -

Table.6.1. List of equipment's.

Sr No	Equipment	Make
1	Extruder	VJ Instruments
2	Dissolution Apparatus	Shimatzu
3	Fourier transform infrared (FTIR) spectrometer.	Brukeropt c Alpha II
4	Spheronizer	
5	Weighing Machine	WENSAR Instruments
6	Ultra violet Spectrophotometer	Lab India Analytical
7	Hardness Tester	Monseto Tester
8	Friability Apparatus	Labline
9	Disintegration Apparatus	Electro lab
10	Tablet Compression Machine	RIMEK Karnawati

Table.6.2. List of excipients.

Sr No	Materials used	Grade	Role
1	Salbutamol sulphate	Industrial	Bronchodilator
2	Magnesium Stearate	Laboratory	Lubricant
3	Talc	Laboratory	Glident
4	Lactose	Laboratory	Diluent
5	MCC	Laboratory	Disintegrant
6	Hydroxy propyl methyl cellulose	Laboratory	Binder

Experimental Work –

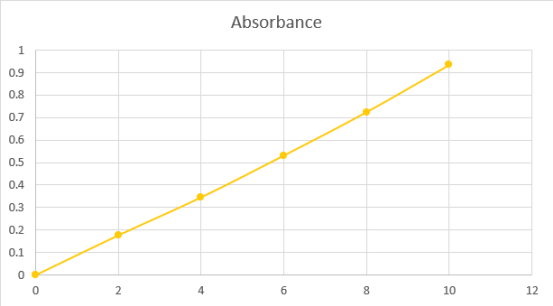
Solubility of Salbutamol sulphate – Salbutamol is nearly insoluble in water, but it is soluble in organic solvents like methanol and chloroform.

- **Standard curve preparation with methanol:** The stock solution had a concentration of 0.1 mg/ml and was made in a 100 ml volumetric flask containing 10 mg of salbutamol and methanol. 0.2, 0.4, 0.6, 0.8, and1ml of the a fore mentioned solution were taken out and blended to make the volume in a10 ml volumetric flask. Its concentration ranged from 2, 4, 6, 8, or 10g/ml. By graphing the average absorbance values Against the relevant drug

concentration, the standard curve for salbutamol was produced.

Table 7.1. Solubility of salbutamol with methnol.

Sr no.	Concentration	Absorbance
1	0	0
2	2	0.177
3	4	0.346
4	6	0.532
5	8	0.725
6	10	0.935



Evaluvation test -

- IPQC tests are routinely run to monitor the process.
- In process tests are performed by production & or quality Control personnel.
- During product development by the formulator.
- Various Official And Non-Official Tests are performed.

A. N**on – Official Tests -**

1. General appearance

I) Organoleptic property

II) Size & Shape

2. Hardness

3. Friability

B. **Official Tests –**

1. Weight Variation
2. Drug Content
3. Dissolution
4. Disintegration

Non official test -

Hardness – The hardness of the tablet was measured using the Monsanto hardness tester. Tablet was placed between two anvils and a force (kg/cm2) was applied. The crushing strength that just caused the tablet to break was recorded.

Fig.7.3. Monsanto hardness tester.

Friability - The friability of the tablets was measured using the laboratory friability apparatus known as Roche friabilator . A pre – weighed sample of tablets was placed in the friabilator and operated for 100 revolutions at the rate of 25 rpm. These tablets were dedusted , reweighed and the percent friability was calculated using the following formulae.

Official Tests –

Weight Variation – From each batch 20 tablets were randomly selected and their average weight was calculated. The individual weight of each tablet was compared with the average weight of 20 tablets. The tablets were said to pass the weight variation test if they complied with the weight variation specifications as per I.P.

Table7.5. Standard of weight variation.

USP Standard	Max. % Difference	BP/IP Standard
130 mg OR Less	10%	84 mg OR Less
130 mg TO 324 mg	7.5%	84 mg TO 250 mg
More than 325	5%	More than 250 mg

Fig 7.5 Weight balance.

Dissolution test -

The dissolution test for salbutamol sulfate tablets commonly utilizes the USP Apparatus II (paddle) method at 50 rpm, with 500-900 mL of 0.1 N HCl or phosphate buffer (pH 6.8) at 37°c +-0.5°c. The drug release is measured using a UV-visible spectrophotometer, typically at a maximum wavelength of 276 nm, ensuring rapid drug release (often >80% within 30-45 minutes).

Fig 7.8 Dissolution apparatus.

DISCUSSION -

Sustained-release matrix tablets are the focus of the present study. The concept of matrix tablets can efficiently and conveniently achieve prolonged drug release. Compared to conventional dosage forms, matrix tablets improve patient adherence, maintain steady plasma drug levels, and minimize the chances of toxicity. Their once-daily dosing regimen also helps reduce overall treatment costs. This approach is beneficial in preventing inappropriate drug usage, particularly antibiotics, and in managing chronic diseases by maintaining drug concentrations within the therapeutic window. Furthermore, it represents a cost-effective strategy.

CONCLUSION

It has been observed that oral sustained-release tablets deliver the drug in a manner distinct from conventional formulations. This approach is effective for achieving therapeutic goals while ensuring optimal patient adherence. However, several physicochemical factors must be carefully controlled. Matrix tablets play a significant role in overcoming the limitations of traditional dosage forms. In addition to their numerous advantages, their cost-efficiency and suitability for once-daily dosing are major benefits. Owing to these key features and enhanced patient compliance, they have the potential to dominate the market and replace conventional alternatives.

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