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Prophylaxis and Prevention of Heart Attack by Pulmonary Delivery of Aspirin by Dry Powder Inhaler

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Abstract

Dry powder inhaler is a device that delivered medication to the lung in the form of a dry powder this device generate an aerosol directly from 1-5 size drug powder or mixture with excipient such as lactose monohydrate The main purpose of this work was to develop dry powder inhaler of aspirin to improve patient compliance by decreasing dose and their side effect as patient is faint and not able to swallow convententional oral tablet where as aspirin always has gastric side effect which can be overcome by delivering aspirin by dry powder inhaler. Aspirin get deposited in alveoli frm where it reaches to systemic circulation and inhibit lipo-oxygenase & prevent heart attack. Various physiochemical property like flow property particle size of drug was determined as particle in the range of 1-5 is suitable for effective alveolar deposition dry powder inhaler was prepared by micronization of aspirin by precipitation method at different concentration of anti solvent stirring speed and temperature. Optimized formulation was evaluated for morphology physiochemical property particle size production yield assay for drug content and in vitro drug release.

Key-Words: Heart attack, Aspirin, Dry Powder

Introduction

Dry powder inhalers (DPIs) are devices through which a active drug containing dry powder formulation is delivered for local or systemic effect via the pulmonary route. This type of drug delivery has several advantages such as rapid drug absorption since most of the surface area resides in the alveolated regions of the deep lung which contain a rich capillary network to facilitate rapid gas exchange. Avoids first pass metabolism. Aspirin is a anti-inflammatory prevent heart attack by inhibiting plat late aggregation

Pulmonary delivery of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The respiratory epithelial cells have a prominent role in the regulation of airway tone and the production of airway lining fluid.

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In this respect, growing attention has been given to the potential of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents, because the high permeability and large absorptive surface area of lungs, (approximately 70-140 m^2 in adult humans having extremely thin absorptive mucosal membrane) and good blood supply[1,2,3].

Material and Methods

Aspirin was a gift sample from Ipca laboratories Ltd (Mumbai, India). Lactose monohydrate was obtained from Merc Chemicals (Mumbai, India). All other chemicals & solvents used were of analytical grade.

Drug excipient interaction study by differential scanning calorimeter

DSC analyze approximately 2 mg of the separate drug and excipient and drug excipient ratio hermetic pans The purpose of multiple heating rates is to determine if the crystalline drug and/or excipient undergo true melting or lose crystalline structure.

Method of Preparation

Aspirin and sulphuric acid were used as reactant with solvent of methanol aspirin (1.8gm) was dissolve in 50ml methanol at 50 with stirring using a magnetic stirrer when aspirin was completely dissolved the

solution was allowed to cool to room temperature according to 1:1 molar ratio the aspirin solution in methanol and sulphuric acid solution were introduced in flask separately and simultaneously the ultra fine aspirin particle were precipitated. When precipitation was complete precipitate were collected by filtration and allow drying over night. The precipitate was then transfer to a vial & sealed.

Preparation of dry powder inhaler

An accurately weighed amount of aspirin was mixed in each case separately with Lactose monohydrate and passed through 60 # mesh and blended in polybag and filled in to size "3" hard gelatin capsules with partial filling manual capsule filling machine with fill weight of 100mg per capsule[4]

Evaluation

Physiochemical property of dry powder

Bulk density tap density angle of repose particle size carr's index of dry powder was determined

Physical appearance

The capsules were visually observed of the particulate matter and for sticky nature of blend inside capsule shell.

Locking length

Locking length were checked with vernier callipers and recorded

Uniformity of Weight

Accurately 20 capsules was weighed individually taking care to preserve the identify of each capsules. the contents of each capsule was removed as completely as possible . capsule was weighed as completely as possible .the emptied shells was weighed individually and for each capsule the net weight of shell was calculated from the respective gross weight and the net content of each individual capsule calculated was Net content of the individual unit

$$(WI)=(W_F-W_E)$$

W_F=weight of the individual filled capsules (mg) W_E=weight of the empty capsules in mg

Moisture Content

50 ml of a mixture of methanol was transferred to the titration vessel and titrate with Karl Fischer reagent to detect any moisture that may present in the formulation 100 mg of powder was , mix and again titrate with the Karl Fischer reagent. Calculate the water content of the specimen, in %, taken by the formula

$$\% \text{ Moisture content} = BF \times 100/W$$

Where, W = Weight of the Sample, in mg. B = (Burette reading) Volume of the KF reagent, in ml. F = the water equivalence factor of KF reagent, in mg.

Particle size distribution

Particle size distribution was determined by stage micrometer 1% suspension of preparation was prepared and evaluated.

Assay (drug content determination)

1.5gm of aspirin precipitate was weighed and dissolved in 15ml ethanol then 50ml of 0.5M NaoH was added it was boiled genetly for 10 min and excess of alkali was titrated with 0.5M hydrochloric acid using phenol red as indicator. Operation was repeated without the substance under examination the difference between the titration represent the amount of sodium required.

1ml of 0.5M NaoH is equivalent to 0.4504gm of aspirin

Scanning electron microscopy

Electron micrographs were taken randomly across the sample using a scanning electron microscope

Particle size

The particle size was measured with Malvern zeta sizer (Malvern Instruments Ltd).

In vitro dissolution

The in-vitro drug release of all the formulations was investigated by dissolution study. An accurately weighed amount of DPI equivalent to 100mg was added to 700 ml of dissolution medium; Phosphate buffer pH 7.4: Ethanol (95%), in 90:10 proportion and drug release was investigated using the USP rotating paddle dissolution apparatus at 100 rpm and 37 ºC. A percent release study was continued from 5 min. to 3 hrs. The samples were withdrawn from the dissolution medium at various time intervals. 5 ml of sample was diluted to 10 ml with dissolution medium and subjected to UV Spectrophotometric analysis at 243nm.

Results and Discussion

The precipitations were affected by reaction temperature, stirring rate, and concentration of sulphuric acid the result are as follow.

Table 1: Aspirin precipitation by different con sulphuric acid

S/No.	Concentration of H_2SO_4 /mol.L⁻¹	% Yield
1	1.5	83.4%
2	2.0	92.3%
3	2.5	93.4%

Table 2: Aspirin Precipitation at Different Stirring Speed

S/No.	Stirring Speed	% Yield
1	300 rpm	84.0 %
2	600 rpm	92.1 %
3	900 rpm	94.0 %

Table 3: Aspirin Precipitation at Different Temperature

S/No.	Te,mperature	% Yield
1	15^{0C}	92.3 %
2	30^{0C}	93.0 %
3	45^{0C}	93.5 %

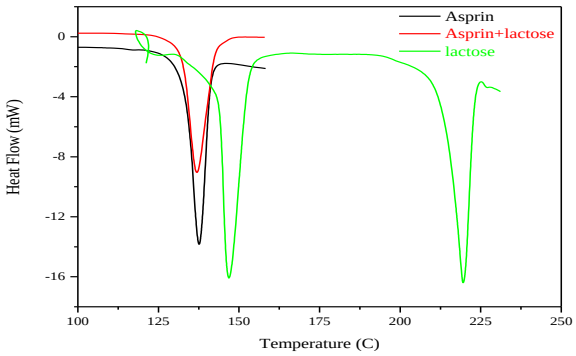

Fig. 1: DSC curve drug excipient compatibility study

Table 4: Physiochemical chemical property of dry powder after precipitation

S/No	Parameter	Result
1	Bulk density	0.392gm/cm³
2	Tapped density	0.66gm/cm³
3	Angle of repose	23.32º
4	Hausner's ratio	1.68
5	Carr's index	68%
6	Particle Size distribution (µm)	4.2µm
7	Moisture content	0.76%

Table 5: Locking length

Batch no.	Percentage lactose	Locking length
1	5%	13mm
2	10%	14mm
3	15%	12mm
4	20%	13mm
5	30%	13mm

Table 6: Weight variation

Batch no.	Percentage lactose	Weight variation
F1	5%	94.5mg
F2	10%	92.3mg
F3	15%	90.2mg
F4	20%	92.1mg
F5	30%	92.5mg

Table 7: Moisture content

Batch no.	Percentage lactose	Moisture content
F1	5%	0.206%
F2	10%	0.36%
F3	15%	0.54%
F4	20%	0.58%
F5	30%	0.61%

Table 8: Assay (Drug content determination)

Batch no.	Percentage lactose	Volume of acid consumed	Percentage drug
F1	5%	20.6 ml	97.66%
F2	10%	19.5 ml	97.58%
F3	15%	18.3 ml	96.96%
F4	20%	17.2 ml	96.83%
F5	30%	15 ml	96.51%

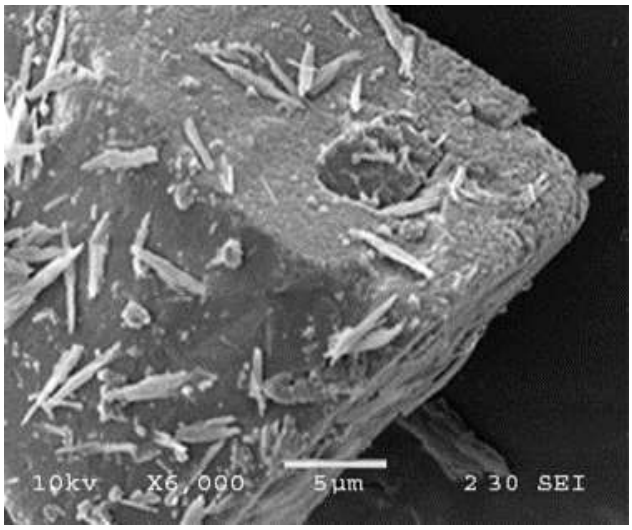

Fig. 2: Scanning electron microscopy of precipitated crystal

Table 9: In vitro dissolution study

S/ No	Time	Absorbance	Conc (µg/ m)	Cumulative concentration	Percent dissolution
1	5min	0.397	1.823	1.823	18.23%
2	30min	0.678	7.333	9.156	73.33%
3	60min	0.718	8.116	17.272	81.16%
4	90min	0.733	8.411	25.68	84.11%
5	120mn	0.740	8.549	34.232	85.49%
6	150mn	0.757	8.882	43.114	88.82%
7	180mn	0.804	9.803	52.917	98.03%

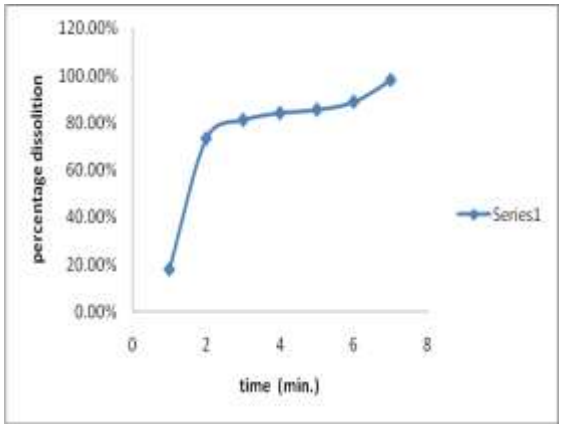

Fig. 3: Dissolution profile

Concluion

The production yield of the formulations was found above 94% The particle size found to be decreasing as after precipitation. The particle size decreased from 5µm to 4.2µm. The drug content in formulation on assay was found to be 97.66%. SEM defined the preparation was crystalline in nature F4 batch show good result in all parameter and selected as optimized batch. The pre compression parameters like bulk density, tapped density, carr's index, hausner's ratio and angle of repose were evaluated and found that DPI possess good flow property Using the precipitation method , the most interesting morphology consisted of clubbed ultra-fine particles of aspirin wasc obtained successfully. The higher concentration of sulphuric acid and stirring rate, and the lower reaction temperature and were favorable for forming smaller particles of aspirin. Using lactose as carrier, the formulation of dry powder inhalation of aspirin was prepared. Particles reached between with th below 3µm narrow distribution obtained respectively. The size range of the particle obtained was suitable to allow pulmonary delivery

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