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Research Paper

Evaluating the Efficacy of Hibiscus Rosa Sinensis Linn Mucilage as Tablet Binder in the Formulation of Orodispersible Tablets of Perindopril Erbumine.

Mr. Patil Pradeep S
R.C. Patel Institute of Pharmacy, Shirpur.
Corresponding Author: - Mr. Patil Pradeep S
R.C. Patel Institute of Pharmacy, Shirpur:-425405
Dhule, Maharashtra

ABSTRACT:
The aim of the current study is to formulate orodispersible tablets of Perindopril Erbumine using a natural binder which was extracted from Hibiscus rosasinensislinn. The leaves of this plant yield mucilage which was used as binder and was extracted using acetone. Perindopril Erbumine an ACE inhibitor was used as a model drug for this study. Perindopril Erbumine is used as an anti-hypertensive agent. It was observed from the evaluations that the batch F_1 showed the best disintegration time and also completes drug release within estimated time. Hence it was concluded that orodispersible tablets of Perindopril Erbumine can be successfully formulated using mucilage extracted from Hibiscus rosasinensislinn as a tablet binder.
***KEY WORDS**: Perindopril Erbumine, Oro-dispersible tablets, Hibiscus rosasinensislinn.*

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I. INTRODUCTION:

Although various novel and advanced drug delivery systems have been introduced for therapeutic use, the popularity of oral dosage forms, particularly tablets have not been eclipsed, because tablets still have numerous advantages, besides others an economical production. Tablets have been facing one basic problem over decades i.e dysphagia, which means it has a disadvantage of difficulty in swallowing when an elderly patient or small children needs to take a tablet.Thus, the orally disintegrating drug delivery system (DDS) is fast dissolving / dispersing, and dissolves in the patient's mouth within a matter of seconds without need of water or chewing. It may therefore be the best solution for patient suffering from dysphasia.Perindopril ter-butyl amine belongs to a group called Angiotensin Converting Enzyme (ACE) inhibitors [1].Inhibition of ACE results in decreased plasma Angiotensin II, leading to decreased vasoconstriction, increased plasma rennin activity and decreased aldosterone secretion. The overall effect of this is a drop in blood pressure and a decrease in the workload of the heart. Perindopril tert-butyl amine is a pro-drug that is hydrolyzed by esterases to the active metabolite Perindoprilat. Perindopril is rapidly absorbed, reaching peak plasma concentration about 1 hour after a single oral dose. Perindoprilat reaches peak plasma concentrations in 2 to 6 hours. The bioavailability of Perindopril is about 70%. The presence of food does not affect the rate and extent of absorption of Perindopril; however, food reduces the conversion of Perindopril to Perindoprilat. [2, 3]

Therefore, the purpose of the present study was to develop a fast disintegrating tablet of Perindopril Erbumine by direct compression using mucilage of Hibiscus Rosa Sinensis as a binder. Such tablet should disintegrate rapidly in the saliva without need of water and release the drug instantly for immediate therapeutic effect.

II. MATERIAL AND METHOD:

Perindopril Erbumine was generously gifted by Hetero drugs Pvt Ltd,Primogel and Ac-Di-Sol were procured from Maple Biotech Pvt Ltd,Manitol was obtained from Oswal chemicals. All other chemicals used were of analytical grade. Fresh Hibiscus plant was obtained from local nursery.

Isolation of mucilage [4]:

The fresh leaves of Hibiscus Rosa sinensis were separated and were washed with water to remove dust and dirt. The leaves were then crushed and were soaked in water for 12 hours, these were then boiled for half hour to separate the mucilage. The solution was passed through double layered muslin cloth, which allowed removal of marc from the filtrate. The mucilage was extracted using acetone in the ratio of 1:3.The extracted mucilage was then dried in oven at a temperature not exceeding 60°C for two hours. The dried powder was then passed through sieve number 80 and was then stored in desiccator until further use.

Preparation of batches of fast disintegrating tablets of Perindopril Erbumine:

For batches perindopril erbumine, mannitol, superdisintegrants, talc, magnesium stearate and mucilage powder were used. Mannitol was used as a diluent and also to impart cooling sensation in mouth. Mucilage of Hibiscus Rosa Sinensis was used as a binder. Superdisintegrants like Ac-Di-Sol and primogel were used for their fast disintegrant action. The concentration of these superdisintegrants was kept between 2-5 %.All ingredients were passed through mesh 250 µm. The ingredients were mixed according to Table.1 Magnesium stearate and talc were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner'sratio [5, 6].The Blend was compressed on 8 mm (diameter) flat punches on a 'Rimek mini press 16 station rotary compression machine. Each tablet weighing 200 mg corresponding to 4 mg of perindopril erbumine were obtained.The tablets were evaluated for weight variation, thickness, friability, hardness and in-vitro disintegration time, wetting time, water absorption ratio and In-vitro dissolution time.

Evaluation of Tablet Properties:

Weight variation [7]: The test was performed according to specifications given in the Ph. Eur., 2004 on 20 tablets. The maximum acceptable limit is ±7.5% deviation of an individual mass from average mass.

Measurement of Tablet Friability [8]: Tablet friability was measured using the Roche Friabilator according to Ph. Eur, on ten tablets each. The friability was determined as the mass loss in percent according to Eq:

$$F= WA-WB/WA .100$$

Where f—Friability, WA—Initial weight (g), WB—Final weight (g). Tablets of friabilities under 1% are acceptable.

Measurement of Tablet hardness:

The crushing strength of tablets was measured by a Monsanto Hardness Tester

Uniformity of Drug Content:

The test is mandatory for tablets with 10mg or less weight of active ingredient[9]**.**Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and powder equivalent to 4 mg of Perindopril was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer pH 6.8. The flasks were shaken to mix the contents thoroughly. The volume was made up to the mark with phosphate buffer pH 6.8 and filtered. One ml of the filtrate was suitably diluted and Perindopril content was estimated at 215.0 nm using a double beam UV-visible spectrophotometer.

Wetting time [10]:

A piece of tissue paper was folded twice and placed in small petri dish containing 6 ml of phosphate buffer (pH 6.8) the tablet was placed on it and the time required for complete wetting of tablet was recorded.

Water Absorption Ratio [11]: A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the paper and was allowed for complete wetting. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation

$$R= (WA-WB) /WB *100$$

Where, WB—Weight of tablet before water absorption, WA— Weight of tablet after water absorption.

In vitro disintegration time (DT) using petri dish method [12]:

10 mL of water at 37 °C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the centre of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of three tablet (n=3) and mean were recorded.

In Vitro Dissolution Study:

Perindopril erbumine tablet test conditions for the dissolution rate studies were used according USP specifications using USP 24, type I apparatus. The dissolution medium was 900 ml of phosphate buffer pH 6.8. The temperature of the dissolution medium and the rate of agitation were maintained at 37±0.5°C and 50 rpm, respectively. Aliquots of 5.0 ml of the dissolution medium were withdrawn at specific time intervals and the volume replaced by fresh dissolution medium, pre-warmed to 37±0.5°C. The drug concentration was determined spectrophotometrically at 215 nm using UV spectrophotometer (shimadzu 1800)

III. RESULT AND DISCUSSION:-

200 grams of leaves of Hibiscus rosasinensis were used for extraction of mucilage. The total yield of mucilage obtained was 6.38%the method used for extraction of mucilage was innovative and assured less utilization of solvent acetone which reduced the extraction cost.

Characterization of powder flow properties:

The powder flow properties were analysed. It was observed that all formulations showed good flow properties with Carr's index ranging from 7.40 to 18.64and Hausner's ratio below 1.25 which indicated good compressibility and flowability.

Characterization of tablet properties of batches:

Orally disintegrating tablets were prepared by direct compression method. A total of twelve formulations were prepared using different superdisintegrants described above. All the formulations passed weight variation test. The hardness of all the tablets containing superdisintegrants was found in the range of 3.4-4.0Kg/cm^2. Friability was found to be below 1% which was an indication of good resistance of tablets. The results of these are shown in table 4 and 5.

In-vitro disintegration time:

Various reports have suggested the unsuitability of conventional disintegrating test apparatus when used for testing the disintegration time of orally disintegrating tablets. This is because of extreme operating conditions in the disintegration test apparatus which fail to provide significant discrimination among the orally disintegrating tablets. Furthermore the conventional disintegration test apparatus employs a relatively huge volume of test solution as compared to the volume of saliva present in human buccal cavity. Therefore the results obtained from conventional disintegration test apparatus do not reflect the actual disintegration time; hence in order to get a better response different method of testing the disintegration time was employed. The disintegration time was measured using a petri plate method as described above. It was found that tablets containing 2.5%, 3.75% and 5% of Ac-Di-Sol, 2.5% and 3.75% of Primogel showed disintegration time within the specified limit. However it was observed that tablets containing 5% of Primogel, required more time to disintegrate.The basic principal that governs the action of superdisintegrantPrimogel is its extensive swelling which was found to increase with the increasing concentration of Primogel above 3.75% as the contact of water with Primogel led to formation of viscous plug. Due to increased viscosity with increased concentration of Primogel it was observed that further uptake may be retarded and the tablets break into large particles instead of disintegrating into smaller particles. This might be the reason for increased disintegration time with increased amount of Primogel.

It was observed that tablets containing 2.5%, 3.75% and 5% of Ac-Di-Sol showed lesser disintegration time when compared with primogelat the same concentration levels. Ac-Di-Sol swells to a larger extent when it comes in contact with water. The fibrous nature of Ac-Di-Sol allows intraparticulate as well as extraparticulate wicking of water at lower concentrations. Ac-Di-Sol is prepared by cross linking of sodium carboxymethyl cellulose, which greatly reduces its water solubility while permitting the material to swell and absorb water several times its mass without losing its fibrous structure. However it was observed that there was a prolongation is disintegration time with concentration of 5%. The reason behind this increased disintegration time may be because of increased viscosity and adhesiveness at higher concentration. As the disintegration time of all batches of tablets containing Ac-Di-Sol showed good disintegration time.

Wetting time:

Wetting time was determined for all the six formulations it was observed that batch F_1showed the wetting time of 61±2 seconds which was less as compared to other batches.It was also observed that the batches containing 2.5% of Ac-Di-Sol showed better wetting time as compared to tablets containing 3.75% and 5% of Ac-Di-Sol.

Water absorption ratio:

Water absorption being one of the important steps in disintegration process it was evaluated. It was observed that with increase in water absorption ration the disintegration of tablets was faster as compared to the tablets with low water absorption ratio. It was observed that the tablets containing 3.75% of Ac-Di-Sol and 10% of Hibiscus mucilage showed highest water absorption ratio of 109.34± 0.752 which was the highest among all other batches.

In vitro disintegration time:

In-vitro disintegration test was carried out using the method described above. It was observed that the disintegration time of all optimized batches was less as compared to the controlled batch. It was also observed that the disintegration time of batch F_1 was the least (69±1 seconds). Thus it was concluded that with lesser concentration of Hibiscus mucilage upto 10 %and 2.5% of Ac-Di-Sol tablets with good wetting time, water absorption ratio and lesser disintegration time

In-vitro dissolution studies:

It was observed that the concentration of binder used within the range of 10 % to 15 % showed 100% drug release within 5 minutes.

IV. CONCLUSION:-

From the evaluations we found that oro-dispersible tablet of Perindopril erbumine containing 10% Hibiscusrosasinensislinn mucilage and 2.5% Ac-Di-Sol gave the best disintegration time and also complete drug release within 5 minutes, the mucilage extracted from Hibiscus rosasinensis assured good binding ability and orally disintegrating tablets of Perindopril can thus be formed successfully by direct compression method.

Table 1: Formulation of batches of fast disintegrating tablets of perindopril erbumine.

Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)
Perindopril Erbumine	4	4	4	4	4	4
Mannitol	167	160	152	167	160	152
Hibiscus Mucilage	20	25	30	20	25	30
Ac-di-sol	5	7	10			
Primogel				5	7	10
Mag- stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

Table 2: Evaluation of powder characteristics.

Sr.no	Formulation	Angle of repose	Bulk density	Tap density	Carr's index	Hausner's ratio
1	F_1	21.19	0.54	0.58	7.40	1.07
2	F_2	23.28	0.51	0.60	17.79	1.21
3	F_3	24.16	0.53	0.6	20	1.17
4	F_4	25.31	0.57	0.625	8.77	1.09
5	F_5	26.17	0.48	0.59	18.64	1.22
6	F_6	26.56	0.47	0.57	17.54	1.21

Table3: Evaluation of batches of fast disintegrating tablets of perindopril erbumine.

Sr.no	Formulation	Weight variation	Friability %	Hardness Kg/cm^2	In-vitro disintegration time (Sec)
1	F_1	Passes	0.40	3.4	69±1
2	F_2	Passes	0.55	3.5	72±2
3	F_3	Passes	0.46	3.5	81±2
4	F_4	Passes	0.35	4.0	73±1
5	F_5	Passes	0.60	3.8	77±2
6	F_6	Passes	0.55	3.5	134±2

Table 4: Evaluation of post compression

Batches	Wetting time (sec)	Water absorption ratio	% drug release ($Q_{5\ min}$)
F_1	61±2	107.43±0.046	100.90±1.85
F_2	69±2	109.34±0.752	101.29±1.46
F_3	76±1.732	99.60±1.105	100.40±0.74
F_4	81±1.527	68.80±0.732	100.30±1.84
F_5	79±0.577	88.32±1.037	99.35±0.70
F_6	114±2	49.40±1.173	94.63±0.65

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