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Formulation and Evaluation of Labetalol Hydrochloride Fast Dissolving Tablets

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ABSTRACT

The purpose of this research was to develop fast dissolving tablets of labetalol hydrochlorideis a phenyl ethanol amine derivative that is a competitive inhibitor at both β_1 and β_2 adrenergic receptors and at the α_1-adrenergic receptor. Labetalol is an antihypertensive drug and the dose is 50-200mg twice/day with food. From the present study, the drug content was uniform in all the labetalol FDT formulations prepared. The drug and super disintegrating agent ratio was found to influence the release of drug from the formulations. As the level of super disintegrating agent and disintegrant changed, the drug release rates were found to be increased in all formulations. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability.

Key words: Labetalol, antihypertensive, super disintegrating agent, fast dissolving tablets.

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INTRODUCTION

Oral drug delivery remains the preferred route for administration of various drugs. Solid dosage forms are popular because of ease of administration accurate dosage, self-medication, pain evasion and most importantly the patient compliance. The faster the drug into solution form, quicker the absorption and onset of clinical effects. Oral dispersible tablets (ODT) are not only indicated for people who have swallowing difficulties, but are also ideal for active people. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablets etc.

Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of fast dissolving dosage forms are increasingly being recognized in both, industry and academics. The basic approach in development of FDT is the use of Superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidon(polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in to the saliva. Swells up to ten fold within 30 seconds when contact water. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Labetalol chemically called as(±)-2-hydroxy-5-{1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl}benzamide, having Molecular Formula - $C_{19}H_{24}N_2O_3$,with Molecular Weight 328.406gm/mol. A white or almost white powder, having Melting Point at 1880C. Sparingly soluble in water and alcohol, but insoluble in methylene chloride. Labetalol is a phenyl ethanol amine derivative that is a competitive inhibitor at both β1 and β2 adrenergic receptors and at the α1-adrenergic receptor. Labetalol is an antihypertensive drug and the dose is 50-200mg twice/day with food.

MATERIALS AND METHODS

Materials

Labetalol is a gift sample from Celon Labs Ltd. Hyderabad. Micro crystalline cellulose, croscarmellose sodium, polyvinylpyrrolidone, sodium lauryl sulphate, sodium saccharin, talc, lactose was obtained from Richer Healthcare Hyderabad. All other the materials used were of

analytical grade.

Preformulation Studies

Tablet Formulations

Different tablet formulations were prepared using direct compression method. Formulations where taken based on the following procedure with different Directly Compressible Vehicle of Excipients for following four formulations.

Table 2: Formulation of Labetalol FDT

Materials For 1 Tablet (mg)	I	II	III	IV
Labetalol	50	50	50	50
Croscarmellose sodium (CCS)	50	75	100	25
Micro crystalline cellulose (MCC)	50	40	30	60
Polyvinylpyrrolidone (PVP K-30)	5	5	5	3
Sodium lauryl sulphate (SLS)	5	5	5	3
Sodium saccharin	2.5	2.5	2.5	2.5
Talc	7.5	7.5	7.5	7.5
Lactose	80	65	50	99

Table 3: Category of Drug and Excipients

S.NO	Ingredients	Category
1	Labetalol	Active ingredient
2	Croscarmellose sodium (CCS)	Super disintegrant
3	Micro crystalline cellulose (MCC)	Disintegrant
4	Polyvinylpyrrolidone (PVP K-30)	Binder
5	Sodium lauryl sulphate (SLS)	Surfactant
6	Sodium saccharin	Sweetener
7	Talc	Glident
8	Lactose	Diluents

Evaluation of Labetalol Tablets

Hardness Test

Tablet requires a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping.16, 17, 18. Tablet hardness has been defined, as the force required breaking a tablet a diametric compression test. The hardness of the tablet was found using Monsanto hardness and Pfizer tester.

Friability

Friability is the loss in weight of tablet in the container due to removal of fine particle from their surface. The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed (initial weight) and transferred into the friabilator. The Friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (final weight). The % friability was then calculated by the following formula

$$F = \frac{Initial\ wt - Final\ wt}{Initial\ wt} \times 100$$

Weight Variation Test

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contain proper amount of drug. Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviated from the average weight by more than limit. The percentage deviation shown in table and none deviated by more than twice the percentage In house specification limit of Percentage deviation of fabricated tablets The results are tabulated in the following table

Disintegration test

The U.S.P. device to test disintegration uses 6glass tubes that are 3" long; open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0C such that the tablet remain 2.5 cm below the surface of liquid on their up ward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have as of the mass.

Content Uniformity

5 tablets were taken and powdered. From that, sample equivalent to 25mgOf drug was taken and transferred to 100ml volumetric flask. Methanol (20ml) was added and gently heated on water bath to dissolve the drug, cool to room temperature and volume was made upto mark with methanol , this was filtered. From the filterate 1ml was taken and diluted with pH 6.8 phosphate buffer and absorbance of this solution was measured as per analytical method.

Assay

Preparation of pH6.8 Phosphate Buffer

27.4gm potassium dihydrogen phosphate was weighed and make up to the volume with 100ml distilled water 8.5gm of NAOH was taken and make up the volume with 100ml of distilled water. From the above solution 50ml of potassium dihydrogen phosphate solution was taken and

39.7ml NAOH is solution was taken and kept in 1000ml volumetric flask and make up the volume up to 1000ml with distilled water.

Procedure of Standard Curve

50mg drug dissolve it in 50ml methanol and from that 10ml was taken in a 100ml volumetric flask and make up the volume up to 100ml with phosphate buffer ph 6.8.This is stock solution of concentration 100µg/ml.

From this stock solution 1ml was taken in 10ml volumetric flask and makes up the volume up to 10ml with phosphate buffer ph 6.8. (1oµg/ml).Respectively solutions of concentrations 10, 20, 30, 40, 50µg/ml was prepared.

Their absorbance was measured in UV visible spectrophotometer and a calibration curve was plotted for time versus absorbance and from that graph standard concentration was determined.

Dissolution Studies

The *in-vitro* drug release studies for all formulations were studied using USP XII type 1(basket paddle type) dissolution rate test apparatus. 900ml of phosphate buffer pH 6.8 solution was used as dissolution medium. The speed of the paddle was set at 50rpm and the temperature of the medium was maintained at 37±0.5^{0}C. 5ml sample were withdrawn at predetermined intervals up to 1hr (60min) and replacements were done with fresh dissolution medium. The samples were analyzed for drug content by UV spectroscopy for comparison, dissolution studies of pure labetalol and commercial labetalol tablets at 302nm which is the λ_{max} of labetalol.

RESULTS AND DISCUSSION

Table 1: Evaluation tests for various formulations of labetalol FDT

Product	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Disintegration Time(sec)	Drug content(%)
F1	3.6	0.399	249.4	20	94
F2	4	0.401	250	23	97
F3	3.8	0.799	250.5	30	99
F4	4.2	0.637	249.8	19	99
Marketed formulation	5.1	0.524	-	208	97

Table 4: Standard Calibration Curve of Labetalol in pH 6.8 Buffer

S.NO.	concentration (µg/mL)	absorbance
1.	0	0
2.	10	0.094
3.	20	0.168
4.	30	0.262
5.	40	0.339
6.	50	0.405
7.	60	0.485

Table 5: Comparative Dissolution Profiles of F_1, F_2, F_3, F_4 And Commercial Product Of Labetalol

CUMULATIVE % DRUG RELEASED					
Time (min)	**F1**	**F2**	**F3**	**F4**	**Commercial product**
5	40.72	41.17	42.97	40.27	18.67
10	50.44	47.77	52.69	49.09	34.22
15	58.60	59.27	61.08	58.37	49.55
20	63.39	62.71	66.99	63.61	62.66
25	67.06	66.83	76.52	67.95	70.83
30	74.56	72.53	89.88	74.33	81.03
40	93.76	96.91	99.65	90.61	89.67
50	-	-	-	99.26	96.75
60	-	-	-	-	-

CONCLUSION

From the present study, the following conclusions are the fast dissolving (oral dispersible) tablets of labetalol using super disintegrating agent and were found to be good without chipping, capping and sticking. The drug content was uniform in all the labetalol FDT formulations prepared. The drug and super disintegrating agent ratio was found to influence the release of drug from the formulations. As the level of super disintegrating agent and disintegrant changed, the drug release rates were found to be increased in all formulations F_1, F_2, F_3,and F_4. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability. Advantages of fast dissolving tablets will surely enhance the patient compliance, low dosing, rapid onset of action and fewer side effects. From the study, it can be concluded that using super disintegrant in tablets showed better disintegration and drug release as compared to normal commercially available labetalol tablets. Prepared formulations were stable during 30 days storage period at room temperature and the bitter taste of labetalol was masked by using sodium saccharine for the patient compliance.Hence, it was concluded that fast dissolving tablets of labetalol can be prepared successfully as (F_4)formulation satisfies all the criteria as an oral dispersible tablet and would be alternative to the currently available conventional tablets.

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