Saudi Journal of Medical and Pharmaceutical Sciences **ISSN 2413-4929 (Print)**
Scholars Middle East Publishers **ISSN 2413-4910 (Online)**
Dubai, United Arab Emirates
Website: https://saudijournals.com/ DOI: 10.36348/sjmps.2017.v03i01.003

Original Research Article

Formulation and Evaluation of Oro-Dispersible Tablets Using Modified Polysaccharides

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Abstract: Orodispersible tablets (ODT) of levocetirizine was prepared using natural polysaccharides *ipomoea batatas* starch, *amorphophallus campanulatus* starch and their modified form by direct compression method and evaluated for their superdisintegrant activity. Levocetirizine dihydrochloride was used as a model drug. The prepared formulations were compared with synthetic superdisintegrants such as crosspovidone and diluent Ludiflash for disintegration and other ODT parameters. FTIR study indicated no interaction between drug and excipients. Precompression parameters, studied for all the formulations were found to be satisfactory. Different concentrations of 2.5%, 5, 7.5% and 10% of modified and unmodified forms of both starches were studied for the improvement in the ODT parameters. The formulations LISN (10%), LISM (10%) (LIS-levocetirizine dihydrochloride+ *ipomoea batatas* starch; N-Natural; M-Modified) and LASN (10%), LASM (10%) (LAS-levocetirizine dihydrochloride+*amorphophallus campanulatus* starch; N-Natural; M-modified) of both the starches showed better DT than lower concentrations. Synthetic superdisintegrant crosspovidone was compared with formulations of natural superdisintegrants. The formulation containing crospovidone 5% concentration showed better DT of 32 seconds compared to natural superdisintegrants, and was used for further comparison of modified polysaccharides. The tablets prepared with Ludiflash as diluent without crospovidone, showed no significant difference in disintegration time. The formulation $LASM_{LU}$ (LAS-Levocetirizine dihydrochloride + *amorphophallus campanulatus* starch; M-Modified; L_u-Ludiflash) showed 95% of drug release compared to other formulations. The release profile of 10% of modified *amorphophallus campanulatus* starch LASM or Ludiflash ($LASM_{LU}$) formulations did not show any significant difference in release profile. Hence in conclusion starch citrate, a new modified starch at 10% or at 5% concentration with crosspovidone with or without Ludiflash as diluent can be used as superdisintegrant for the preparation of orodispersible tablets.

Keywords: Levocetirizine-dihydrochloride, Oro-dispersible tablets, direct compression, ipomoea batatas starch, amorphophallus campanulatus starch

INTRODUCTION

Orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. These are the best suitable for the drugs that are to be given to unconscious, pediatric, geriatrics and in the emergency conditions where the patient compliance and immediate release are required [1].

The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as a solid dosage form containing medical substances which disintegrate rapidly usually within a matter of seconds, when placed upon the tongue [2].

The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. Though several directly compressible excipients are available, there is a continued need to develop new, safe and effective excipients for direct compression method [3].

A widely prescribed drug belongs to BCS class III and exhibit high solubility and low permeability. Levocetrizine dihydrochloride is an orally active H1-receptor antagonist. It is indicated for the relief of symptoms associated with perennial allergic rhinitis and for treatment of the uncomplicated skin manifestations of chronic idiopathic utricaria in adults and children 6 months of age and older [4].

Studies have shown that the properties of some starches have been improved by physical and chemical modifications [5].

The objective of the present study is to prepare and evaluate starch citrate, a new chemically modified starch, as a directly compressible vehicle for tablets. Acid modified starches are produced commercially by hydrolyzing the starches. Acid hydrolysis of starch involves the cleavage of the glucosidic bonds between the monomeric units which involves both protonation of the glycosidic oxygen and addition of water to yield the reducing sugar end group (D-glucose) of the starch. This process diminishes the molar mass and increases the solubility and relative crystallinity of the starches. The properties of excipients that ensure a robust and successful directly compressible adjuvant with good flow ability, good compressibility, low lubricant sensitivity, and high dilution potential. The choice of excipients becomes critical in terms of its functionality as regards direct compression and rapid disintegration abilities [6].

MATERIALS AND METHODS

MATERIALS

Levocetirizine dihydrochloride was gift sample from Dr.Reddy's Laboratories Ltd, Hyderabad, Starch citrate was prepared in the laboratory, Citric acid (SD fine Chemicals Limited), *ipomoea batatas* starch (Yarrow chem. Products), *amorphophallus campanulatus* starch (Yarrow chem. Products), Ludiflash (Mylan laboratories) Methanol crosspovidone, lactose, talc, magnesium stearate were procured from commercial sources.

METHODS

Preparation of Starch citrate

METHOD 1

Starch citrate was prepared based on the method of Klaushfer et al[7]with some modifications. Citric acid (20 g) was dissolved in 20 ml of water, the pH of the solution was adjusted to 3.5 with 10 M sodium hydroxide and finally the volume was made upto 50 ml by adding water. The citric acid solution (50 ml) was mixed with 50 g of natural starch in a stainless steel tray and conditioned for 16 h at room temperature (28˚C). The tray was then placed in oven and dried at 60˚C for 6 h. The mixture obtained was ground and further dried in hot air oven at 130˚C for 2 h. The dry mixture was repeatedly washed with water to remove unreacted citric acid. The washed starch citrate was further dried at 50˚C to remove the moisture completely. The product obtained was ground and sized.

METHOD 2

Starch citrate was prepared by reacting starch with citric acid at elevated temparatures. When citric acid is heated, it will dehydrate to yield an anhydride. The citric anhydride can then react with starch to form starch citrate. The reactions involved are shown in fig-1:

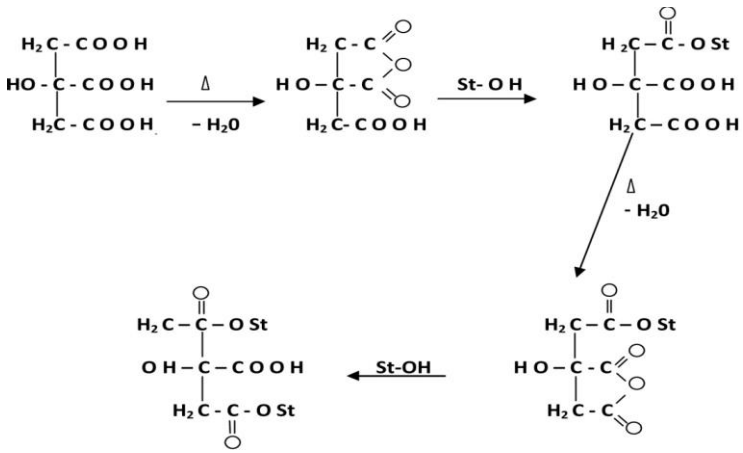

Fig-1: Starch-Citric acid reaction

Characterization of Starch citrate

The starch citrate prepared was evaluated for the following:

pH: The pH of a 1% w/v slurry was measured.

Viscosity [8]

Viscosity of 1% dispersion in water was measured using Ostwald Viscometer.

Swelling index [9]

Starch citrate (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

$$\text{Swelling Index (SI)} = \frac{\text{Final volume} - \text{Initial volume}}{\text{Initial volume}} \times 100$$

Test for gelling property [10]

The gelling property (gelatinization) of the starch citrate prepared was evaluated by heating a 2 g of the dispersion in water at 100˚C for 30 min.

Bulk density: Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

Angle of repose: Angle of repose was measured by fixed funnel method.

Compressibility index: Compressibility index (*CI*) was determined by measuring the tapped density and bulk density after hundred tapings of starch citrate in a measuring cylinder. CI was calculated using equation:

$$\textbf{C.I (\%)} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \times 100$$

Table-1: Formulation design of modified and unmodified starches

Composition	LISN/ LISM	LISN/ LISM	LISN/ LISM	LISN/ LISM	LASN/ LASM	LASN/ LASM	LASN/ LASM	LASN/ LASM
	Mg							
Drug	5	5	5	5	5	5	5	5
Lactose	42.25	41	39.75	38.5	42.25	41	39.75	38.5
ISN/ISM ASN/ASM	1.25(2.5%)	2.5(5%)	3.75(7.5%)	5(10%)	1.25(2.5%)	2.5(5%)	3.75(7.5%)	5(10%)
PVP K30	1	1	1	1	1	1	1	1
Mg st	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Talc	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total wt	50	50	50	50	50	50	50	50

Table-2: Formulation design of modified and unmodified starches with Ludeflash as diluent in comparison with crosspovidone

Ingredients	$LISN_{LU}$/ $LISM_{LU}$	$LASN_{LU}$/ $LASM_{LU}$	CP (2.5%)	CP (5%)
	Mg			
Drug	5	5	5	5
Ludiflash	41	41	42.25	41
ISN/ISM ASN/ASM	2.5(5%)	2.5(5%)	1.25(2.5%)	2.5(5%)
PVP K30	1	1	1	1
Mg stearate	0.25	0.25	0.25	0.25
Talc	0.25	0.25	0.25	0.25
Total weight	50	50	50	50

Preparation of tablets by direct compression method

Compressed tablets each containing 5mg of levocetirizine dihydrochloride drug using 4.76 mm punch on a Rimek-1 rotary tablet machine by direct compression method.

Evaluation of Tablets

All the tablets prepared were evaluated for content of active ingredients, hardness, friability, and disintegration time and dissolution rate as per official (IP) methods. Hardness of tablets was tested using Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time was determined in a USP dissolution test apparatus using water as test fluid.

Thickness and Diameter

The thickness and diameter of the prepared tablets were measured using Vernier Caliper. It is expressed in mm.

Weight Variation

Weight variation was determined by weighing 20 tablets individually; the average weight and percent variation of tablet was calculated individually.

Hardness and Crushing Strength

Hardness was determined by taking ten tablets from each formulation, using a Monsanto tablet hardness tester and the average of applied pressure (kg/cm2) for crushing the tablet was determined.

Friability

The friability of the tablet was determined by elactrolabe Friabilator. Initially weighed (Wo) 20tablets after dusting and placing them in a friability tester, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablets (Wf) was recorded and the percent friability was calculated by

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish containing 6ml of water. A tablet was placed on the paper and the time taken for complete wetting of tablet was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

Water absorption ratio

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 the time required for complete wetting was measured. The wet tablet was weighed.

Water absorption ratio R, was determined using following equation

$$R = Wa - W\,b\,/Wb \times 100$$

Where Wa = weight of tablet after absorption
Wb = weight of tablet before absorption

Disintegration time

Disintegration time was measured using a modified disintegration method. For this purpose, a Petri dish was filled with 10 ml of water at 37ºC±0.5ºC. The tablet was carefully put in the centre of the Petri dish and the time for the tablet to completely disintegrate into fine particles was noted.

***In- vitro* disintegration time**

Disintegration times of six tablets randomly selected from each batch was individually determined using Erweka disintegration tester containing purified water at 37 ± 0.5˚C.The mean disintegration was calculated.

Estimation of drug content in the tablets

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 5 mg was weighed and dissolved in 100 ml of 6.8 pH phosphate buffer. This dispersion was filtered and 1 ml of the above solutions were taken and diluted to 10 ml with 6.8 pH phosphate buffer and the drug content was estimated at 233 nm spectrophotometrically using the standard calibration curve.

***In-vitro* Dissolution rate study**

Dissolution rate of levocetirizine dihydrochloride from the tablets prepared was studied in phosphate buffer pH 6.8 (900 ml) employing USP 8 station dissolution rate test apparatus with a paddle stirrer at 50 rpm. One tablet containing 5 mg of levocetirizine dihydrochloride was used in each test. A temperature 37±1˚C was maintained throughout the test. Aliquots of Samples of dissolution medium (5 ml) were withdrawn and volume was adjusted by the buffer. Aliquots following suitable dilution were analysed spectrophotometrically at 233nm.

RESULTS AND DISCUSSIONS

Starch citrate

Physicochemical properties of the starch citrate were shown in the table 3. The starch granules showed semi crystalline structure. The prepared starch citrate was found to be off white color and semi crystalline nature. The semi crystalline nature further conformed by DSC. The melting point of the starch citrate was determined by using melting point apparatus. Powder that passes through mesh no 80 and retained on mesh no 120 was collected. Native starch was hydrolyzing upon heating and converted to gel/ paste and it was not found in case of the starch citrate.

Table-3: Physicochemical properties of the starch citrate prepared

Property	Result
Solubility	Insoluble in all aqueous and organic solvents tested
pH	7.16
Viscosity	1.10cps
Gelling property	No gelling and the swollen particles of starch citrate separated from water. Whereas in the case of starch, it was gelatinized and formed gel.

Chemically modified starch had good swelling property without pasting when heated in water was consider to be promising carrier for ODT's tablets enhancing the dissolution rate[7].

Fourier Transform Infrared spectroscopy

FTIR spectra of the drug, citric acid, natural starch and modified starch were shown in below figures. levocetirizine dihydrochloride gives the peak IR spectrum near by at 3546/cm^{-1} due to O-H stretching, 2979/cm^{-1} due to C-H stretching, 2947/cm^{-1} due to C-H stretching ,1745/cm^{-1} due to C=O stretching, 1598/cm^{-1} due to C-C stretching. Hence there was no incompatibility between the drug and excipients used in the study.

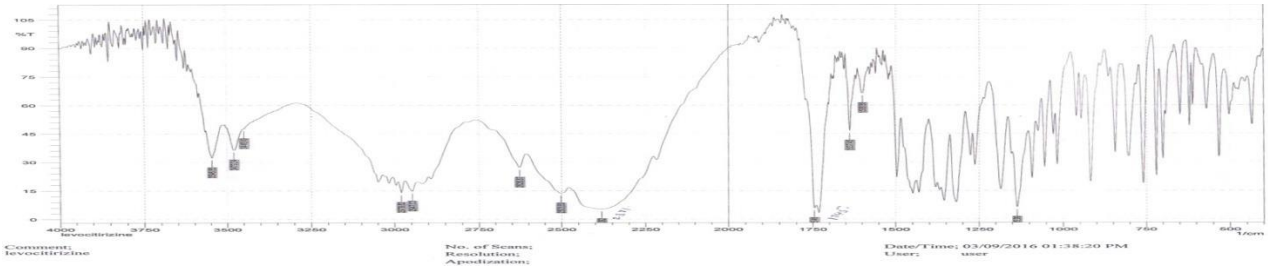

Fig-2: FTIR spectra of the drug

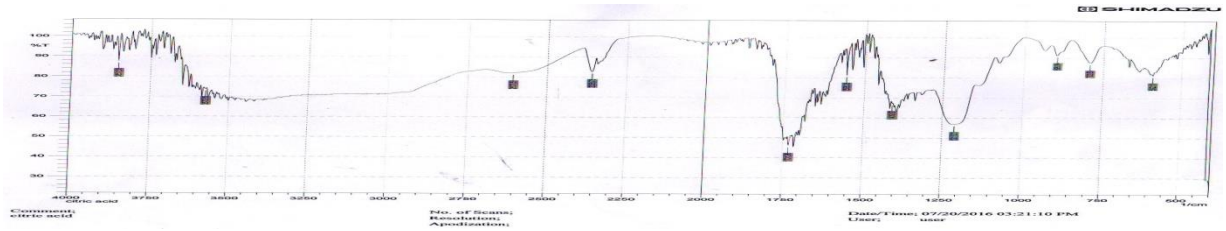

Fig-3: FT-IR of citric acid

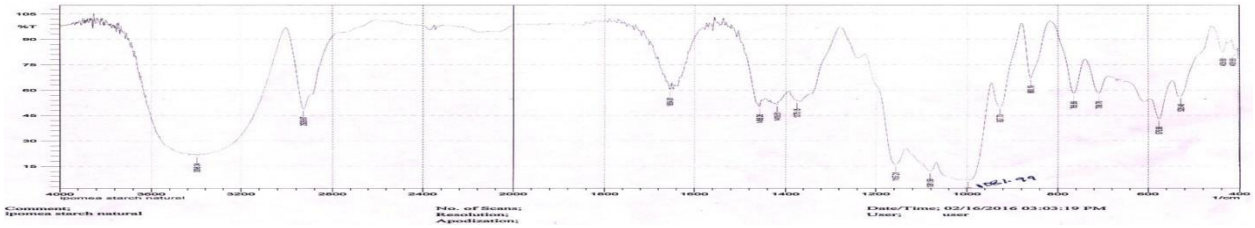

Fig-4: FT-IR of *ipomoea batatas* starch

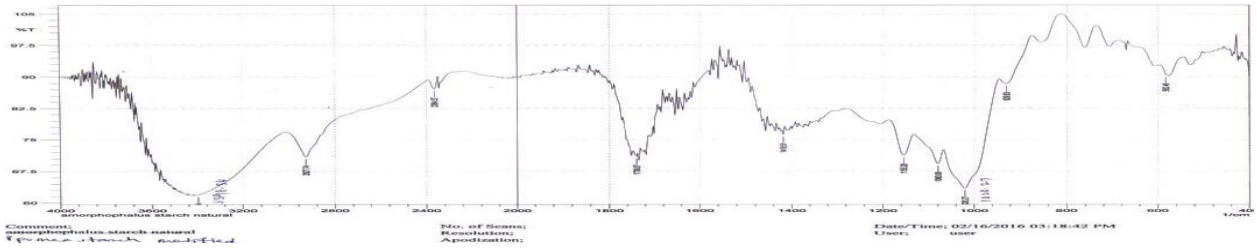

Fig-5: FT-IR of modified *ipomoea batatas* starch

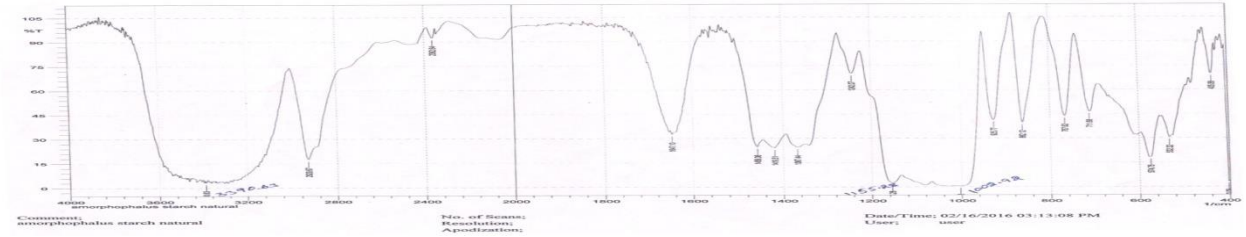

Fig-6: FT-IR of *amorphophallus campanulatus* starch

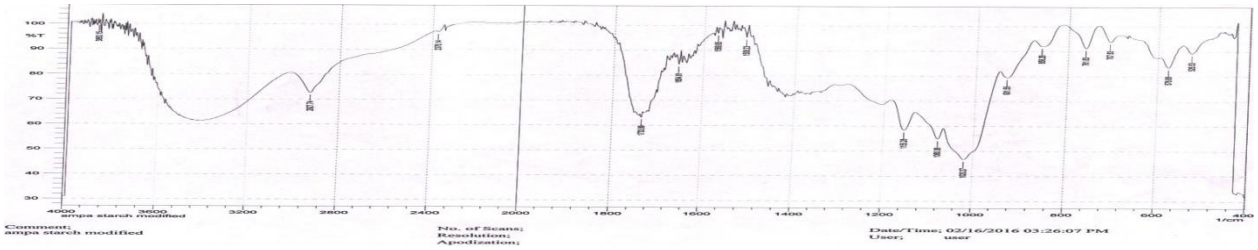

Fig-7: FT-IR of modified *amorphophallus campanulatus* starch

Differential Scanning Calorimetry

The DSC thermograms of the citric acid and natural and modified *ipomoea batatas* and *amorphophallus campanulatus starches* were shown in below figures. The melting point of the citric acid and both natural and modified starches were determined by using DSC apparatus. The citric acid showed the melting point at 160.4˚C. Natural and modified form of *ipomoea batatas* starch showed the melting point at 113.6˚C, 114.8˚C. Natural and modified form of *amorphophallus campanulatus* showed the melting point at 112.5˚C, 177.8˚C.

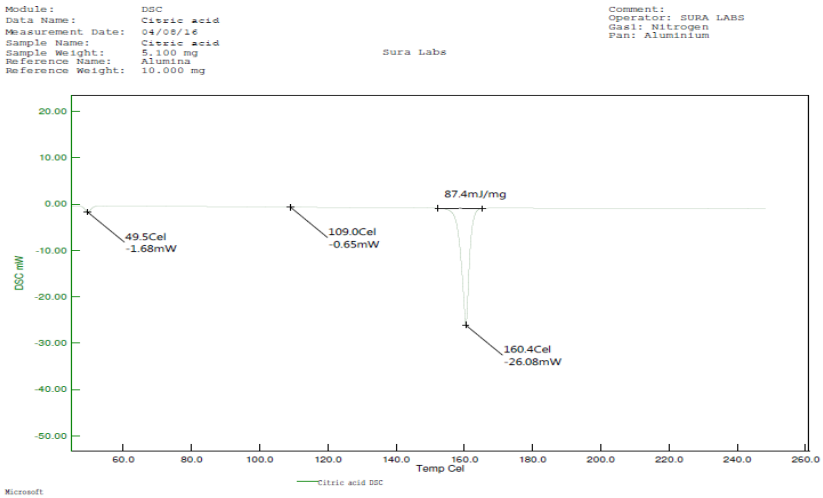

Fig-8: DSC graph of citric acid

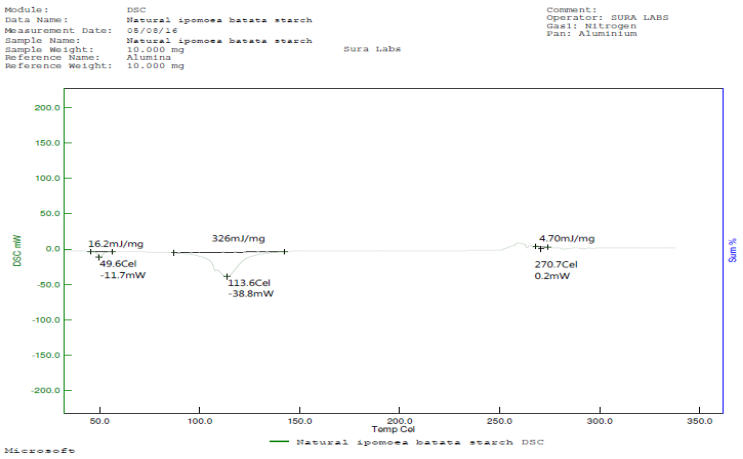

Fig-8: DSC graph of *ipomoea batatas*

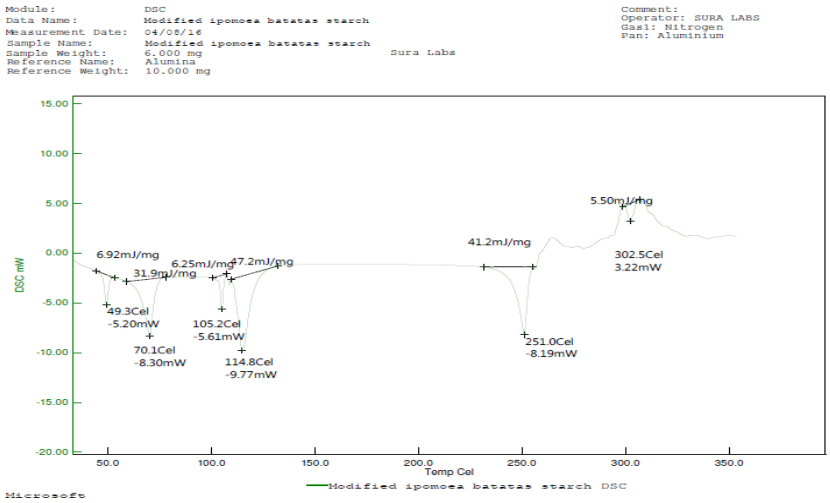

Fig-9: DSC graph of modified *ipomoea batatas*

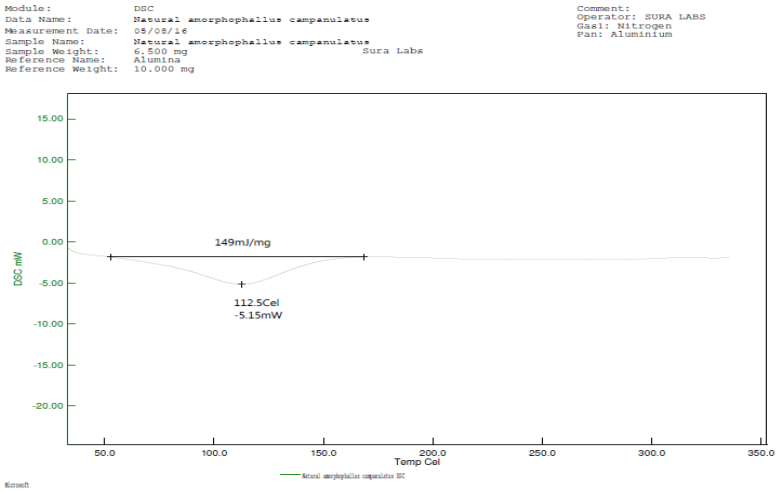

Fig-10: DSC graph of *amorphophallus campanulatus*

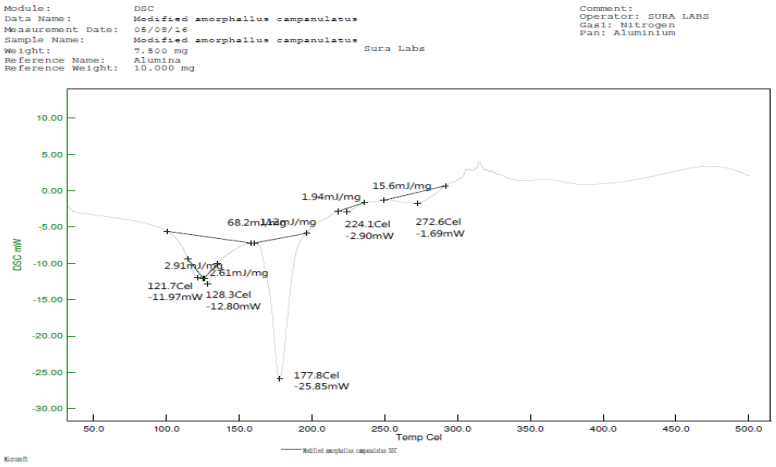

Fig-11: DSC graph of modified *amorphophallus campanulatus*

Table-4: Evaluation of optimized ODT of levocetirizine formulations

Formulation	Weight variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio	Content uniformity (%)
LISN(2.5%)	49±0.40	2.3±0.12	2.1±0.14	0.01±0.40	120±0.29	75±0.35	20±0.21	98.12±0.81
LISM(2.5%)	50±0.16	2.4±0.12	1.9±0.12	0.03±0.08	110±0.81	80±0.40	30±0.37	99.08±0.76
LISN(5%)	50±0.81	2.2±0.47	2.0±0.13	0.016±0.56	100±0.32	60±0.81	30±0.24	99.24±0.53
LISM(5%)	48±0.29	2.3±0.81	2.0±0.81	0.023±0.08	88±0.58	75±0.24	34±0.81	99.31±058
LISN(7.5%)	50±0.24	2.1±0.16	2.0±0.26	0.07±0.18	80±0.16	37±0.32	34±0.16	99.56±0.31
LISM(7.5%)	49±0.81	2.2±0.14	1.9±0.21	0.08±0.08	55±0.29	42±0.48	40±0.21	99.65±0.13
LISN(10%)	50±0.29	2.4±0.81	2.2±047	0.01±0.40	45±0.43	29±0.16	40±0.16	99.70±0.14
LISM(10%)	50±0.41	2.3±0.94	2.0±0.12	0.04±0.56	40±0.50	35±0.49	50±0.28	99.81±0.11
LASN(2.5%)	48±0.53	2.2±0.24	1.9±0.81	0.72±1.05	125±0.48	50±0.65	24±0.40	99.10±0.21
LASM(2.5%)	50±0.45	2.3±0.81	2±0.16	0.08±0.01	105±0.57	53±0.73	26±0.58	99.13±0.61
LASN(5%)	50±0.37	2.3±0.14	2.1±0.14	0.06±0.21	75±0.53	45±0.61	30±0.69	99.26±0.71
LASM(5%)	49±0.61	2.4±0.81	2.2±0.29	0.05±0.04	65±0.77	48±0.88	34±0.65	99.37±0.74
LASN(7.5%)	50±0.48	2.2±0.21	2±0.81	0.08±0.21	56±0.73	35±0.57	36±0.61	99.46±0.69
LASM(7.5%)	49±0.16	2.3±0.16	2.1±0.35	0.07±1.05	50±0.45	38±0.65	50±0.10	99.56±0.73
LASN(10%)	50±0.40	2.2±0.35	1.9±0.29	0.31±0.01	45±0.57	28±0.64	44±0.61	99.69±0.78
LASM(10%)	50±0.10	2.4±0.81	2.2±0.21	0.18±0.04	40±0.65	32±0.61	60±0.50	99.80±0.94
CP(5%)	50±0.53	2.3±0.81	2.1±0.43	0.72±1.05	32±0.40	24±0.53	48±0.25	99.82±0.50
$LISN_{LU}$	49±0.67	2.2±0.12	2.0±0.29	0.19±0.01	45±0.36	38±0.14	42±0.35	99.19±0.68
$LISM_{LU}$	50±0.25	2.3±0.08	1.9±0.45	0.31±0.01	35±0.58	35±0.28	55±0.57	99.36±0.34
$LASN_{LU}$	49±0.16	2.2±0.39	2.1±0.69	0.16±1.05	48±0.69	28±0.69	46±0.49	99.64±0.77
$LASM_{LU}$	50±0.34	2.4±0.75	2.2±0.54	0.45±0.21	38±0.85	26±0.75	60±0.29	99.85±0.88

All the above formulations were evaluated for various parameters like hardness, friability, drug content, wetting time, water absorption ratio, disintegration time and *in-vitro* drug release studies. The hardness of the tablets was found to be 2 to 3 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 1.9 to 2.2. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e., 10%.

The LISN and LISM formulations (2.5%,5%,7.5%,10%) showed disintegration time between 120 to 40 sec. LISN(10%) & LISM(10%) formulations were showed better DT of 45 and 40 seconds respectively. The unmodified and modified *ipomoea batatas* starch LISN(10%) & LISM(10%) formulations showed less DT compared to other formultions. The wetting time was found to be range 75 to 29 seconds. The wetting time of unmodified *ipomoea batatas* starch at different concentrations showed lower values compared to other concentrations. This is because the aqueous medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bonds and breaks the tablet into fine particles. The Wetting time decreases with increase in the concentration of super disintegrants [7]. The water absorption ratio was found to be 20 to 50. The drug content was found to be 98.12 to 99.81%, indicating uniform distribution of drug in the tablets.

CP (5%) formulations showed better DT value 32 seconds. This may be due to crospovidone particles appear granular and highly porous. This unique, porous particle morphlogy facilitates wicking of liquid into the tablet and particles to generate rapid disintegration[8]. Due to it's high crosslink density, crospovidone swells rapidly in water without gelling. The wetting time was found to be range 24 to 62 seconds. This may be due to higher ability of swelling and also higher capacity of absorption of water [8]. The water absorption ratio was found to be 26 to 54. The drug content was found to be 98.27 to 99.82%, indicating uniform distribution of drug in the tablets.

The formulations with ludiflash both modified and unmodified starches showed disintegration time Between 35 to 48 sec.

The $LISM_{LU}$ & $LASM_{LU}$ formulations showed wetting time in the range of 38 to 26 seconds. The wetting time of modified $LISM_{LU}$ & $LASM_{LU}$ formulations showed lower values compared to $LISN_{LU}$ & $LASN_{LU}$ formulations. This may due to Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient[11]. The water absorption ratio was found to be 60 to 42. The $LISM_{LU}$ & $LASM_{LU}$ formulations showed less DT compared to $LISN_{LU}$ & $LASN_{LU}$ formulations,because the Formulations with Ludiflash, had high retention capacity of water and was due to Incorporation of co-processed materials(90% mannitol,5%Kollidon (crospovidone) and 5% Kollicoat (polyvinyl acetate)

lead to a notable increase in water absorption rate which was reflected on a rapid disintegration time[12]. The drug content was found to be 99.19 to 99.85%, indicating uniform distribution of drug in the tablets.

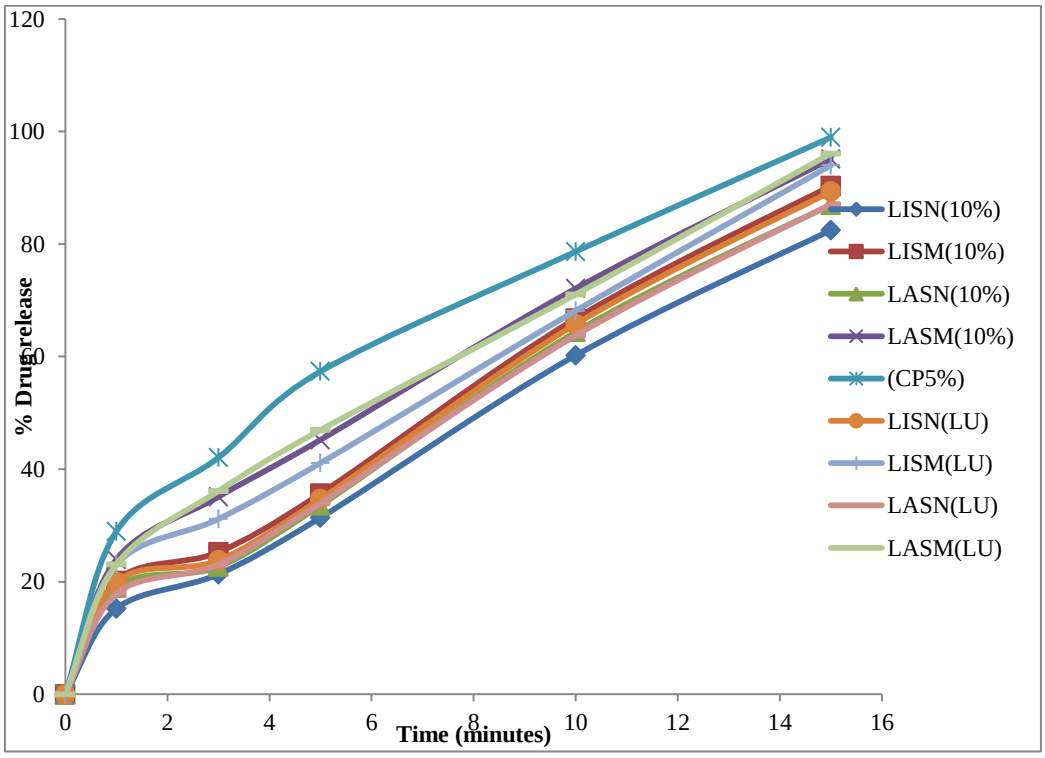

Fig-12: Dissolution profile of levocetirizine dihydrochloride tablets by direct compression method

In vitro release of drug

The above figure depicts the *in-vitro* dissolution of formulations of levocetirizine dihydrochloride tablets with LISN (10%), LISM (10%), LASN (10%), LASM (10%) and CP (5%).The formulation with 10% of modified *amorphophallus campanulatus (LASM)*starch showed better release of 95.09% of the drug in 15 minutes as compared to formulations with 10% of both natural and modified *ipomoea batatas* and *amorphophallus campanulatus* starches.

Formulation with CP (5%) showed better dissolution when compared to other formulations. The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. The formulaton ($LASM_{CP}$) showed better release of 95.95% of the drug in 15 minutes as compared to other formulations.

From the result it is found that, the formulations with higher concentrations (10%) of both natural and modified starches showed higher superdisintegrant activity compared to lower concentrations. The formulation CP5% showed better disintegration. The formulation $LASM_{LU}$ showed 95% of drug release compared to other formulations. The release profile of 10% of modified *amorphophallus campanulatus* starch LASM or Ludiflash ($LASM_{LU}$) formulations did not show any significant difference in release profile.

Hence in conclusion starch citrate, a new modified starch at 10% or at 5% concentration with crosspovidone with or without Ludiflash as diluent can be used as superdisintegrant for the preparation of orodispersible tablets. Hence it can be a promising superdisintegrant for the preparation of tablets by direct compression.

CONCLUSION

The present work described a study on formulation and evaluation of ODT of levocetirizine dihydrochloride, which were prepared by using natural polysaccharides such as *ipomoea batatas* starch and *amorphophallus campanulatus* and their modified forms by using starch citrate.Both the starches were modified by acid hydrolysis method.

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