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COMPARATIVE STUDY AND EVALUATION OF THE DISINTEGRATING PROPERTY OF STARCH DERIVED FROM *CUCURBITA MAXIMA* PULP AND OFFICIAL CORN STARCH IN TELMISARTAN TABLET

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ABSTRACT

The aim of this study was to evaluate the disintegrating property of the *Cucurbita maxima* starch (pumpkin) in formulation of Telmisartan tablet. Starch powder was extracted and characteristics have been studied .FTIR spectral study shows no interaction between the active ingredient and excipients in newly developed tablet formulations. A total of eleven formulations was prepared, with different concentrations of starch derived from *Cucurbita maxima* pulp and comparatively consisting of official corn starch as disintegrant. F11 consist of partially pre-gelatinized starch of *Cucurbita maxima* in the concentration of 77.5%. All formulations were prepared by wet granulation method, except for F11, by direct compression. Standard pre-compression evaluations were done prior and standard post-compression evaluations after the tablet punching. The eligible formulations were further tested for drug uniformity, *In-vitro* disintegration time and *In-vitro* dissolution to determine the percentage of drug release. The result proves that a lesser amount of *Cucurbita maxima* starch is required as disintegrant (10%) w/w, than corn starch to show the best disintegrating activity. F11 on the other hand has the potential to be developed into orodispersible tablets in future for its fast disintegrating property

KEY WORDS: *Cucurbita maxima* starch, Comparative study, Disintegration, Telmisartan

INTRODUCTION

Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant or superdisintegrant and its consistency of performance are of critical importance to the formulation development of such tablets [Vimal V.V.*et.al.,* 2013]. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants . In more recent years, increasing attention has been paid to formulating fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth.[V.P Pandey.*et.al.*,2014] Disintegrants are substances or mixture of substances added the drug formulation that facilitate the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants . Super-disintegrants are generally used at a low level in the solid dosage form, typically 1 – 10 % by weight relative to the total weight of the dosage unit.

It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of interrelationships between these major mechanisms. Until fairly recently, starch was the only excipient used as a disintegrant. To be effective, corn starch has to be used in concentrations of between 5-10%. Below 5%, there is insufficient “channels” available for wicking (and subsequent swelling) to take place. Above 10%, the incompressibility of starch makes it difficult to compress tablets of sufficient hardness. Although the connection between bioavailability of drug and tablet disintegration took some time to become appreciated, it is now accepted that the role of the disintegrant is extremely important. [G.Ramu.*et.al.,* 2010]

Native starches are extensively used as a disintegrant in tablets. Their action passes via an immediate swelling when wetted with aqueous liquids. Starches are isolated from raw materials of different botanical origin and they have therefore different

physicochemical properties such as particle size or humidity. These differences could modify their functionality as tablet filler and disintegrant. Starch constitutes an important class of tablet disintegrant and was rated among the top ten pharmaceutical ingredients by the International Joint Conference on Excipients . Corn and potato are the official starches most commonly employed in tablet production. Although starches from various other botanical sources have been investigated , information on *Cucurbita maxima* pulp starch as disintegrant appears to be scanty in the literature.

The plant Cucurbita maxima Duchesne (commonly known as pumpkin) belongs to the family of Cucurbitaceae is widely cultivated throughout the world for use as vegetable as well as medicine. Despite its presumed safety, acceptance as pharmaceutical grade starch would require detail investigation and submission of supportive data ascertaining the safety, efficacy, stability and compatibility with candidate drugs and other formulation additives. In this paper, the fundamental and derived properties of *Cucurbita maxima* starch powder that are of importance in pharmaceutical application are presented. In addition, a comparative disintegration time and dissolution rate of Telmisartan tablets formulated with *Cucurbita maxima* starch powder and corn starch powder are reported.

In tablet formulation, native starch possesses many desirable filler properties but it has poor flowability and compressibility. The latter two parameters have a particular importance for direct compression tablets. Furthermore, the filler should yield tablets of adequate crushing strength withpout having to apply an excessive compression force [Rahul V. Manek.*et.al.,* 2012]. In comparison with DC excipients, native starches exhibit lower total degree of packing during both die filling (zero pressure) and at low pressures as a result of rearrangement process before an appreciable amount of interparticulate bonding takes place. In this respect, there is a need to improve the phase rearrangement by modifying the surface structure, particle size and shape of the native starch. [Owolabi.*et.al.,* 2010]

MATERIALS AND METHODS

Materials

Telmisartan was obtained as a gift sample from YSP .Sdn.Bhd. , Cucurbita maxima fruit was purchase from Selayang local market and Corn Starch powder, Soluble Starch powder,Lactose, Magnesium Stearate, Talc, Sodium Hydroxide and Methanol was purchased from R&M Chemicals, Malaysia. The drug analysis was done using UVSpectrophotometer (Jasco,Japan and V-630). Roche Friabilator, Dissolution USP Apparatus, Dissolution USP Apparatus, and Disintegration Test Apparatus used for evaluation studies were obtained from Electrolab. Rotary Tablet Punching Machine from Mini Tablet Press was used in this study.

Methadology

Extraction of *Cucurbita maxima* starch powder

Cucurbita maxima fruits (pumpkin) are purchased from local wholesale market in Selayang and authentication was obtained from University Putra Malaysia (UPM) prior to preparation. Later, after confirmation has been done, the pumpkin was cleaned with water to remove dust from the surface and further peel was removed. The seeds were removed as well and was cut into small pieces and soaked in water overnight to leach the cyanogenic glycosides present. The water was decanted, pumpkin was milled to pulp and distilled water was added to dilute the slurry . The pulp was separated from the blended pumpkin by means of a muslin cloth and agitation was provided using hands. The obtained starch suspension was allowed to settle under gravity for 12hours and then the supernatant was decanted. The sediment was centrifuged at 3000rpm for 25 minutes. The upper protein layer was scrapped off and the starch suspension obtained was washed several times using three times its volume of water for three days with intermittent shaking and changing of water. [Mohammed Iqdam.*et.al.,* 2013]. Purification of starch was done using isopropyl alcohol. The starch was then dried at 40^{o}C in hot air oven, sieved stored in dessicator for further used. Percentage yield was calculated.

Pre-compression evaluation

Evaluation of powder properties of *Cucurbita maxima* starch

Identification tests for the presence of starch

BP starch identification test- 1g of starch is boiled with 15mls of water. After cooling to 1ml of the mucilage, 2 drops of 0.1N iodine solution was added and colour change was observed

Organoleptic Evaluation of Isolated starch.

The isolated mucilage was characterized for organoleptic properties such as color, odor, taste, and texture.

Solubility Behavior mucilage.

One part of dry starch powder was shaken with different solvents and the solubility was determined

pH of starch powder

The starch powder was weighed and dissolved in water separately to get a 1%w/v solution. The pH of solution was determined using digital pH meter.

Hydration capacity

1g of starch was placed in 15ml centrifuge tube ,10ml distilled water was added. Contents were shaken for 2 mins ,allowed to stand for 10minutes and centrifuged at 1000rpm for 10 mins. Supernatant decanted and the wet mass was weighted.

Hydration capacity = Ws/Wd

Where Wd and Ws are weight of dry sample and weight of sediment respectively.

Swelling capacity of Isolated starch powder.

The tapped volume occupied by 10g of each starch (Vd) in 100ml measuring cylinder was noted. The powder was dispersed in 85ml of distilled water and volume made up to 100 with more water. After 18hours, the volume of sediment (Vw) was estimated and swelling capacity and swelling index is computed. [Okunlola .*et.al.,* 2011]

Swelling capacity: Vw-Vd

Swelling index = Vw/Vd

Where: Vd and Vw are initial volume of material before hydration and volume of hydrated material, respectively.

Determination of pH

The pH of 1% solution of *Cucurbita maxima* starch was determined using digital pH meter at 37°C.

Loss on drying

The moisture content *Cucurbita maxima* starch was determined using a modification of a method specified in the B.P (1993) for acacia. A weighed quantity of each sample was transferred into a petri dish and then dried in an oven at 105°C until a constant weight was obtained. The % moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage.

Standard Calibration Curve of TELM in Phosphate buffer pH7.5

Telmisartan 10 mg was accurately weighed. The drug was dissolved in methanol and volume was made to 100 mL to obtain a stock solution of 100 µg/mL. Different aliquots of this solution were diluted suitably with pH 7.5 buffer to give solutions containing 3, 6, 9, 12, 15 and 18 µg/mL of Telmisartan. The absorbance of these solutions was measured at 296 nm on UV-Visible spectrophotometer against pH 7.5 buffer as blank. The standard curve was performed in triplicate. The linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations.

[Pratikkumar A. Patel. *et. al.,* 2010]

Fourier Transform Infra Red (FTIR) analysis

The FTIR study was done at University Malaya Chemistry Laboratory. The FTIR spectrum of Telmisartan was recorded between the scanning range of 4000 – 400 against wave number (cm- 1) and % Transmittance. Samples were prepared in KBr discs (2mg sample in 200mg KBr) with a hydrostatic press at a force of 5cm- 2 for 5 min and the resolution was 4 cm - 1.

Preparation of granulation

Wet granulation method was used for formulations 1-10. Active ingredient and disintegrant were mixed for 5mins. 5% of binder mucilage was added little by little and massed for another 5 minutes. The damn mass was then passed through 1.7mm sieve and

allowed to dry. Then, it was passed through 1.66mm sieve and dried again. Prepared granules were stored according to formulations in desiccator for further use.

Direct compression method was used for formulation 11 to check for compressibility of partially pre-gelatinized starch.

Evaluation of granules

Angle of repose

The angle of repose was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation :

Tan $\theta = h/r$;Where h = height of the powder cone; r = radius of the powder cone.

Bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity 8g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2 cm for 30 times. The tapping was continued until no further change in the volume was noted. LBD and TBD were calculated using the following formulas [Gauhar. *et al*., 2011]

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Hausner's index

This was calculated as the ratio of tapped density to bulk density of the samples.

H.R= TD/BD

Preparation of tablets

Tablets containing 40 mg of Telmisartan were prepared and the different formulae employed in the study are shown in table 1.

The granules prepared were compressed using rotary tablet punching machine fitted with 8.00 mm concave faced punch and die set possessing 6 metric ton compression force. Before compression, the surface of die and punch were lubricated with magnesium stearate and 1.5 % talc was added into the granulations. [Karan Malik.et.al., 2011].Tablets were then stored over silica gel for 24hours to allow for elastic recovery and hardening.

Table 1 : Formulation code table of the formulated tablet Batches

Form.	Drug (mg)	CMS (mg)	CS (mg)	SP (mg)	Lactose (mg)	Mgs (mg)	Talc (mg)	Total (mg)
1	40	40	-	10	105	2	3	200
2	40	30	-	10	115	2	3	200
3	40	20	-	10	125	2	3	200
4	40	10	-	10	135	2	3	200
5	40	-	40	10	105	2	3	200
6	40	-	30	10	115	2	3	200
7	40	-	20	10	125	2	3	200
8	40	-	10	10	135	2	3	200
9	40	145	-	10	-	2	3	200
10	40	-	-	10	145	2	3	200
11	40	155 (PPG)	-	-	-	2	3	200

Post-Compression Evaluation

Evaluation of Tablets Weight variation

All prepared tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and mean and standard deviation was calculated [The United States Pharmacopoeial Convention, 2007].

Friability

Tablets of all batches were used to evaluate friability as per USP XXIV monograph. Friability testing was done by Roche Friabilator with readings in triplicate.

Hardness

Hardness of all batches was determined using Digital Force Gauge (Model:EL=500N, Electrolab). The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets.

Thickness

The thickness of the tablets was determined using vernier caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations, with standard deviations.

Determination of Disintegration Time

The tablets were placed in each of the six tubes of the basket of the disintegration apparatus using water as the immersion fluid. The test was carried out for 30 minutes. The disintegration time was noted when no residue of the unit, except fragments of insoluble coating, remained on the screen of the apparatus.

Drug content

TELM content in the tablets was estimated in triplicate using the UV method. Drug content was assessed for six randomly selected tablets from each batch. The tablets were crushed and total content of the six tablets was mixed thoroughly. The powder weighed for 40mg tablet was 50mg of crushed tablet powder (equivalent to 10mg of TELM) was transferred to 100ml volumetric flask. Then, 50ml of methanol was added and allowed to sonicate for 15-20mins and the volume was made up to mark with methanol. The solution was then filtered through a Whattman filter paper. The filtrate was diluted suitably with the solvent to get the solution of 10µg/ml concentration. The absorbance (296nm) was measured against blank solution. The concentration of drug content in each tablet was calculated by using the standard curve. [Pratikkumar A.Patel *.et.al.,* 2010]

Dissolution Profile Study

The protocol followed for the dissolution study of Telmisartan tablets was as depicted in Table 4.4. [Pratikkumar A.Patel *.et.al.,* 2010]

Table 2: Protocol for dissolution studies

Apparatus	USP TypeII Dissolution testing Apparatus
Speed	75rpm
No of tablets	6 units
Dissolution media	Ph buffer 7.5 (900ml)
Samplaing interval	5,10,15,30,45,60
Sampling volume	5ml
Replesnishing fluid	Ph buffer 7.5
Temperature	37^{o}C +/- 0.5 ^{o}C
Analytical method	UV Spectrophotometry (ƛmax= 296nm)

Statistical analysis

The cumulative percentage releases of Telmisartan from tablets were calculated. Their statistical significance was tested using ANOVA. A value of $p<0.05$ was considered statistically significant.

RESULTS

Evaluation of powder characteristics of *Cucurbita maxima starch*

Table 3 : Evaluation of powder properties of *Cucurbita maxima* starch

Solubility test	: Cold water: not soluble : warm water: partially soluble : 95% ethanol: not soluble
pH test	: 6.8
Organoleptic evaluation	:Yellowish white, fine powder, smooth texture, warm bland taste , odorless
Iodine test	: Dark blue colour is seen. Presence of starch is confirmed.
Hydration capacity	: 2.12g/ 1.0g = 2.12g
Swelling capacity	: 35ml-15ml = 20ml
Swelling index	: 35/15ml = 2.33
Pasting temperature	: 45.7 ºC
Moisture content/loss on drying	: (3g-2.7138)/ 3g x 100 = 9.54%
Percentage yield	: 10.5mg/569.24mg x 100 = 1.84%

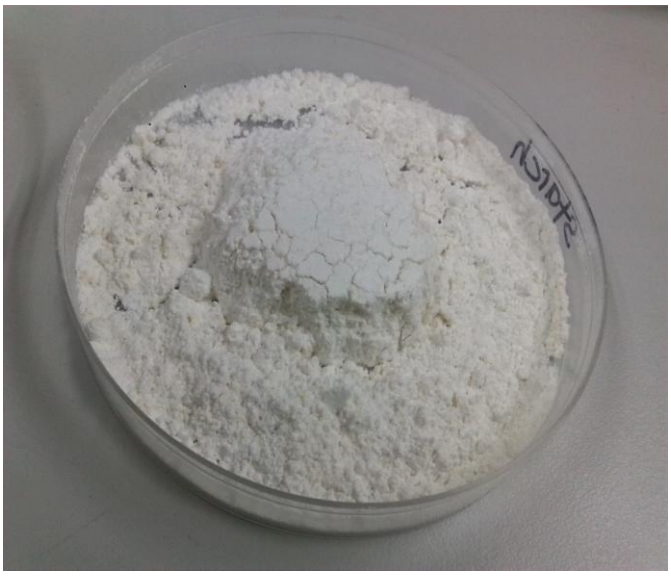


Figure 1: *Cucurbita maxima* starch powder

Pre-compression Evaluation Studies

Table 4: Pre-compression evaluation for F1-F11

Formulation code	Angle of repose (º)		Carr's index (mg/ml)		Hausner's ratio	
	Mean	±SD	Mean	±SD	Mean	±SD
F1	25.17	0.52	5.78	0.31	1.06	0
F2	27.10	0.23	6.59	1.09	1.09	0.04
F3	25.60	1.05	5.50	0.40	1.06	0.01
F4	25.07	0.06	6.09	0.19	1.06	0.01
F5	29.07	0.51	7.32	0.37	1.08	0.01
F6	26.22	0.46	5.69	0.13	1.06	0
F7	26.21	0.62	5.31	0.64	1.06	0.01
F8	28.73	0.38	6.17	0.42	1.06	0.01
F9	25.44	0.21	6.06	0.54	1.06	0.01
F10	32.40	0.35	5.94	0.17	1.06	0.01
F11	25.12	0.59	5.88	0.28	1.06	0

Post- compression evaluation

Table 5: Post-compression evaluation for F1-F11

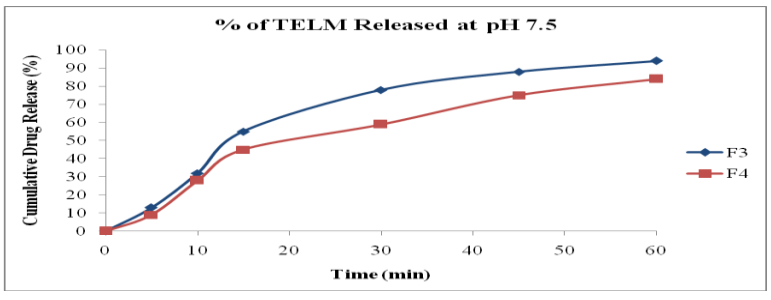
Formulation code	weight variation (mg)		Friability (%)		Hardness (N)		Thickness (mm)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
F1	196.827	7.26631	2.04	0.04	17.23	0.25	3.98	0.01
F2	194.859	7.93281	1.04	0.01	27.77	0.57	3.97	0.01
F3	191.16	6.9103	0.9	0.02	30.73	1.21	3.98	0.01
F4	191.878	8.32916	0.82	0	29.2	2.17	3.98	0.01
F5	189.2	7.76644	1.05	0.05	17.83	0.45	3.97	0.01
F6	187.987	9.60063	0.98	0	26.97	0.4	3.99	0.01
F7	196.603	8.23575	0.83	0.02	29.57	0.68	3.98	0.01
F8	190.928	9.41407	0.66	0.04	32.27	2.2	3.98	0.01
F9	193.458	8.92823	3.85	0.49	21.13	2.19	3.98	0.02
F10	189.291	7.93372	0.54	0.01	33.73	2.49	3.99	0.01
F11	192.422	8.00591	0.8	0.05	28.19	0.97	3.98	0.02

Table 6: Disintegration time and drug content uniformity of F3, F4, F6, F7, F8, F10, and F11

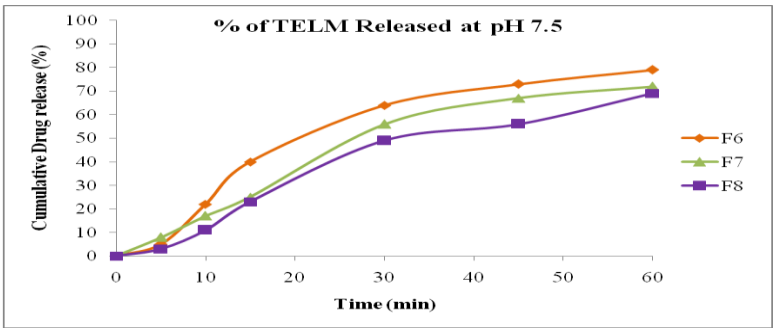
Formulation code	Disintegration time (min)		Drug content	
	Mean	± SD	Mean (mg)	±SD
F3	14.39	0.69	38.33	0.61
F4	16.13	1.16	38.35	0.32
F6	10.59	0.47	37.57	0.4
F7	32.63	2.3	38.59	0.34
F8	31.31	2.29	37.61	0.33
F10	39.31	4.93	38.23	0.24
F11	1.13	0.63	38.09	0.69

Table 7: Percentage of drug release of F3, F4, F6, F7, F8, F10, and F11

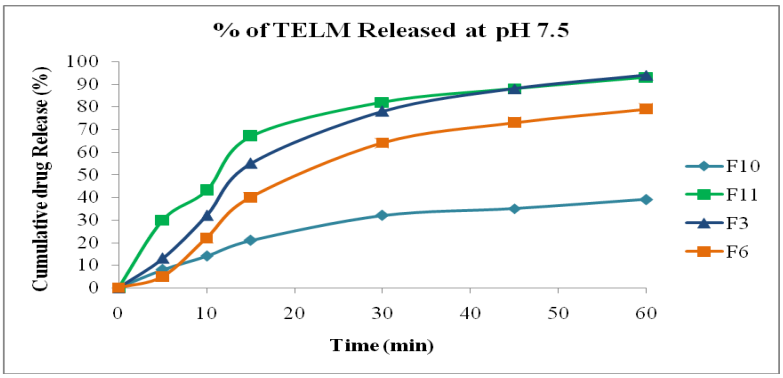
Time (minutes)	% Cumulative Drug Release						
	F3	F4	F6	F7	F8	F10	F11
5	13.57	9.39	5.32	8.29	3.19	8.37	30.5
10	33.39	29.21	23.42	17.62	11.69	14.67	44.15
15	57.39	46.94	42.58	25.91	24.45	21.99	69.35
30	81.39	61.54	68.14	58.04	52.1	33.5	85.1
45	91.83	78.23	77.72	69.44	59.54	36.64	91.4
60	98.09	87.62	84.11	74.62	73.37	40.83	96.65



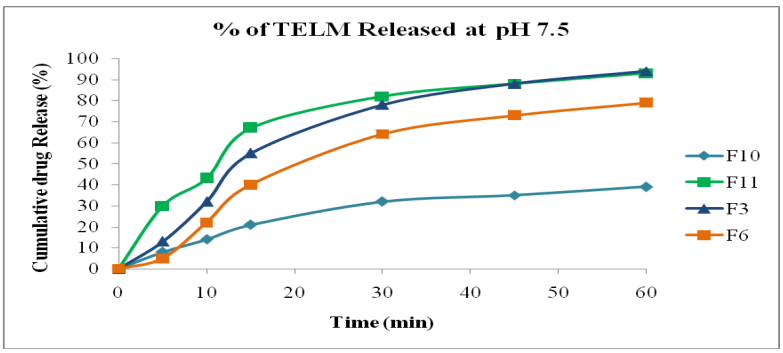
Comparative drug dissolution profile of F6, F7, F8



Comparative drug dissolution profile of F6, F7, F8



Comparative drug dissolution profile of F3, F6, F10, F11



Comparative drug dissolution profile of F3, F6, F10, F11

DISCUSSION

In this study, attempts have been made to evaluate the disintegrating property of the *Cucurbita maxima* starch (pumpkin) in formulation of Telmisartan tablet. A total of eleven formulations have been prepared, where F1-F4, consisting of 5%, 10%, 15%, 20% w/w of starch derived from *Cucurbita maxima* pulp as disintegrant, F5-F8, comparatively consisting of official corn starch as disintegrant, in the parallel concentration. Corn Starch formulations being the oldest disintegrant ,are chosen for this study because of its standard use in comparative studies .72.5% of *Cucurbita maxima* starch powder is used in F9 to study if it has a dual property as both disintegrant and filler in tablet. F10 is of no composition of any disintegrant and therefore serves as a

placebo for the rest of the formulations. F11 on the other hand, consist of partially pre-gelatinized starch of *Cucurbita maxima* in the concentration of 77.5% , to study if it can serve multiple purpose as excipient and whether the formulation can be prepared by direct compression method. F1-F10 are all prepared by wet granulation method.

The isolation of starch from pulp of *Cucurbita maxima* was relatively straightforward. Starch granules settled easily, and this settling was not hampered by the presence of non-starch materials from the pumpkin. The non-starch materials remained suspended in the supernatant liquid and were decanted off. Purification was done on the extracted starch to reduce the possibility of the presence of non-starch materials and microbial contamination. The yield of *Cucurbita maxima* starch, after extraction of was found to be approximately 10.5mg per 569.24mg of fresh pumpkin. This 1.84% yield was considered satisfactory.

Starch occurs in plants as granules generally, which are further characterized in size, shape, and morphology. As these characteristics are determined by the biological origin, an evaluation on powder characteristics was carried out for *Cucurbita maxima* starch. The starch was found to be a yellowish white, odorless powder with a warm bland taste and smooth texture. Observation under optical microscope shows that *Cucurbita maxima* starch exhibits elliptical to spherical granules with a relatively smooth surface.

To be potentially useful as a pharmaceutical excipient, the ability of starch granules to swell has important implications. Swelling power is not only a measure of the hydration capacity of the sample but is also indicative of the associative forces in the granules. The swelling capacity, index and hydration capacity is shown in Table 5.1. As demonstrates, the swelling index is fairly acceptable and high enough to exhibit disintegrating activity of the starch. Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism by which certain disintegrating agents (such as starch) impart their disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to break apart [Carter. *et al.,* 2006]. At ambient temperatures, starch swelling is viewed as a property of amylopectin whereas amylose acts as diluent. The solubility test carried out shows that *Curcubita maxima* starch is not soluble in cold water and 95% ethanol, however is partially soluble in warm water. The pH test resulted in pH6.8 which is close to neutral, which was why alkalization of starch was not required after extraction. The dark blue colour appearance upon iodine drops confirmed the presence of starch in the extraction and the intensity of the colour showed that there is no presence of any non-starch components. The pasting temperature of *Cucurbita maxima* starch was found to be 45.7^{o}C. At this temperature, it is said that stach begin to gelatinize. The gelatinization temperature of starch depends upon plant type and on the degree of cross-linking of the amylopectin. Below the gelatinization temperature, partial pre-gelatinization takes place. [Starch/Stärke.*et al.,*2013]. Above this temperature, full gelatinization takes place and thus, starch becomes completely soluble. The lower moisture content of the *Cucurbita maxima*, which is 9.54% starch indicate it less prone to microbial attack, less ability to interact with drugs that are moisture sensitive and high ability to absorb water to facilitate disintegration. [Olayemi.*et.al*.,2008]. High moisture may lead to activation of enzymes and proliferation of microorganisms.

For the selection for analytical wavelength, 10µg/ml solution of TELM was prepared by appropriate dilution of standard stock solution and scanned in spectrum mode from 400 to 200nm .From the spectra of the drug, a clear peak can be obtained at 296nm was selected for analysis. This indicates that the drug is of good purity and as well is supported by previous literature [Komal Patel.*et.al.,* 2011]. The standard curve was performed in triplicate. The linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations. The calibration curve of TELM in phosphate buffer 7.5 is shown in Figure 5.1. This graph was then used to estimate unknown concentrations, in drug uniformity test and dissolution test, by using the obtained value of absorbance in UV spectrum.

As a general rule, the FTIR spectroscopic studies were carried out by using FT/IR-6000 series FTIR spectrometer and the vibrational frequency bands were espressed in terms of wave numbers (cm^{-1}). in the current investigation, telmisartan was used as an active pharmaceutical excipient (API) for developing new formulations. Based on the FTIR spectral data of the drug, excipient (*Cucurbita maxima* starch) and drug plus excipient, we could derive the following

CONCLUSIONS

The –C=O- characteristic vibrational stretching frequency band of Telmisartan at 1694cm^{-1}, was clearly identified in the FTIR spectrum of newly developing formulations. This observation could be the remarkable spectral property indicating no existence of interaction between the drug and the excipient. As one can see from the other FTIR vibrational frequency bands obtained , most of it have been reproduced with similar wave numbers (cm^{-1}), suggesting the existence of TELM drug in its original form in the formulation.In overview, the developed new formulations have gained some insights for future studies. Hence, it was proposed worthwhile to conduct pharmacokinetic studies such as absorption, distribution, metabolism and elimination of drug.

Preparation of granules were made by wet granulation method to increase the flow properties and compressibility of the tablet. This is because, generally, native starch have very low flow property because they exist as fine powders which adheres to the funnel or have higher cohesive forces between the particles. In order to make it easier to flow, formulations containing starches have to be granulated, forming spherical granules, which flows easily. Wet granulation processing still maintains drug product processing dominance, because it is less dependent on excipient performance attributes. However, it involves multiple manufacturing steps, which can add time and cost to the development process. Therefore, whilst wet granulation was necessary for F1-F10, an attempt was made to modify *Cucurbita maxima* starch by thermal partial gelatinization, which was then dried and powdered, forming semi-crystalline structures. With such modification being made to starch in F11, direct compression with acceptable compressibility was made possible at the end of this study.

An angle of repose was obtained as in Table 5.3. F1 to F11 respectively, all fall within the required range for pharmaceutical powders which is 25º-45º. [Musa *et. al*, 2004]. The angle of repose values in the range of 25– 30° and 31–35° indicate excellent and good flow properties for the material, respectively. If the value is greater than 40°, it suggests poor flow of the material. From the results obtained, it can be seen that almost all the batches of formulations has angle of repose at lower range , indicates a better flow property. The mean difference is significant at P-value<0.05. Angle of repose has been used to characterized the flow properties of powders, it also also related to inter-particulate friction or resistance to movement between particles [Shiihii *et. al*, 2011].

In addition, the angle of repose and other derived properties of the powders namely bulk density and tapped density depends on the particle size distribution, particle shape, and tendency of the particles to adhere together. The results of the Tap density, bulk density, Carr's index and Hausner's index are tabulated in Table 5.4, 5.5, 5.6 and 5.7 respectively. It was found from the tabulation, when compared to the standard range stated in British Pharmacopoeia (BP), that all the batches of formulations fall in the range , where C.I are less than 10% and Hausner's ratio, within 1.00-1.11, indicating excellent flow properties of granules. The mean difference is also significant at P-value<0.05.

40 tablets per formulation were punched using the rotary punching machine. Tablets prepared by both wet granulation and direct compression methods were found to be good without any chipping, capping and sticking. Prepared tablets were evaluated for weight variation and percentage deviation from the average weight are found to be within (±7.5) the prescribed official limits. The mean difference is found to be significant at P-value<0.05.The thickness of the tablets were all uniform from F1-F11 as can be seen from Table 6.1 , where it fall from 3.97mm-3.99mm . The hardness of the tablet were tested using the digital gauge in newton, N. It can be observed from Tablet 6 that the amount of force needed to break the tablet is indirectly influenced by the percentage concentration of disintegrant present in the formulation. Higher percentage of starch component in a formulation makes the tablet less harder, probably because of the less compressibility and elastic deformation nature of native starch. The crushing strength required, increased in formulations based on the disintegrant concentration as 72.5%<20%<15%<10%<5%. F11 however has comparatively lower hardness compared to F3, F4, F7 and F8 and F10 probably because it contains *Cucurbita maxima* starch in partially pre-gelatinized form and that is directly compressed without the need to add granulating fluid/paste as binder. The mean difference is of tablet hardness is found to be significant at P-value<0.05. The friability test has been carried out for all the batch of tablet formulations and results are tabulated in Table 5.9. This test is additional to check crushing strength of tablet and by this test, one can also check capping or lamination .When compared to USP limit which is within 0.5 to 1%, only

F3, F4, F6, F7, F8, F10 and F11 could be considered for further testing. The mean difference is also significant at P-value<0.05. However, F1, F2, F5 and F9 are found to be not eligible as tablets because of their friability exceeding the limit.

The *in vitro* disintegration time of Telmisartan tablets prepared by wet granulation method (F3, F4, F6, F7, F8, F10) were found to be in the range of 10 to 39 minutes. The mean difference too is significant at P-value<0.05. Generally, uncoated tablets disintegrate around 15 minutes, in water with Disc at $37^0C \pm 2^0C$. The result therefore is interesting which coincidentally, was the focal point of the present study. It can be concluded from the obtained results that, F3 with 10% concentration of *Cucurbita maxima* starch as disintegrant has shown an optimum disintegration time, compared to the rest of the formulations. The disintegration time is also faster when compared with the same concentration of corn starch (10%) as disintegrant , in F7. As for F11, the tablets were found to disintegrate within 1min 13 sec. This gives the possibility for the formulation containing partially pre-gelatinized starch of *Cucurbita maxima* to be considered in the formulation of oro-dispersible tablets. However, further study needs to be done to evaluate the formulation such as wetting time and etc.

The USP (Telmisartan tablets Revision bulletin, 2011) requires the mean content of TELM in TELM tablets to be not less than 95% and not more than 110%. The mean contents of TELM in all the tablets were within the required range as shown in Table 6.3, except F6 and F8, where the drug content is 93.93% and 94.02% respectively. The mean difference is however found to be significant at P-value<0.05 . The lesser drug content could be due to the wet granulation method being used for these formulations, where some wastage of API can take place in the process unexpectedly.

The *in vitro* dissolution study provides the dissolution cumulative release graph that shows the dissolution profile of the various batches containing varying concentrations of disintegrants. The BP stipulates that 70% of drug should be released within 30 minutes for uncoated tablets. Only formulation containing 10% of *Cucurbita maxima* starch as disintegrant met this specification, although others released about 70 % of their drug content after 40 minutes. *Cucurbita maxima* starch performed better at 10% w/w over time whereas for corn starch best performances was achieved with a higher concentration of 15% w/w. This result suggesting that lesser amount of *Cucurbita maxima* starch is required compared to corn starch to give an optimum disintegration and dissolution profile to the TELM tablet formulation. The only formulation which gave more than 70% release within 30mins and is more consistent in drug release pattern comparable to F3 is, F11. This may be due to formulation characteristics of the product, which contains partially pre-gelatinized starch which made the formulation to be able to be prepared by direct compression method. With respect to compression properties, partial pre-gelatinization increases the densification of starch during the die-filling of the matrix at lower compression pressures. It also facilitates a quicker onset of plastic deformation of starch, but it decreases its extent during the compression. All the rest of the dissolution curves obtained did not match the BP specifications and also did not show a consistent pattern of drug release. The mean difference is however found to be significant at P-value<0.05.

CONCLUSION

The present study was carried out to determine if *Cucurbita maxima* starch has disintegrating property comparable to corn starch. A total of elevent formulations were prepared using Telmisartan as the model drug, where F1-F10 were prepared by wet granulation method, and F1 by direct compression. All the formulations prepared have passed the pre-compression evaluation studies, therefore were successfully punched into tablets. However, post- compression evaluation studies have resulted in the elimination of few batches of formulations , mainly due to its friable nature. Formulation that were not continued to disintegration test, drug content uniformity test and dissolution test include F1, F2, F5, F9. Among the formulations that were tested with further evaluation studies, F3 with *Cucurbita maxima* starch as disintegrant of 10% w/w concentration shows comparable disintegration time and percentage of drug release with F6, of 15% w/w corn starch as disintegrant. This proves that a lesser amount of *Cucurbita maxima* starch is required as disintegrant ,than corn starch to show the best disintegrating activity in a tablet formulation. F11 on the other hand has disintegration time within 1mins, and drug release almost the same as F3 . Since it is prepared by direct compression method, F11 found to have more benefit over F3, where further studies can be done to formulate orodispersible tablets .

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