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Formulation and Evaluation of Orodispersible Tablets of Diltiazem Hydrochloride Using Musa Paradisiaca (Banana Powder) As Natural Superdisintegrant

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ABSTRACT
Over the last few decades demand for development of orally disintegrating tablet has enormously increased as it has significant impact on the patient compliance.Oro dispersible tablets offer great advantage for people with dysphagia (difficulty in swallowing) and institutionalized patients.Diltiazem hydrochloride is a drug of choice for hypertension, angina pectoris and some types of arrhythmias.The present study was aimed at preparing tablets of Diltiazem hydrochloride using banana powder as natural superdisintegrant and comparing its effect with other synthetic super disintegrants like sodium starch glycolate and cross carmellose sodium.Six formulations were prepared using different concentrations (5% and 10%) of three superdisintegrants. The powder blend prepared for compression was evaluated for precompression parameters like bulk density,tappeddensity,Hausners ratio, compressibility index and angle of repose.The result obtained indicated that all the powder blends were having good properties for preparing tablets by direct compression technique.Tablets were prepared by direct compression using rotary tablet machine to a target average weight of 200mg.The prepared tablets were evaluated for various post compression parameters like hardness, weight variation, friability,disintegration and dissolution tests.The tablets were also subjected to wetting studies,water absorption studies and invitro dispersion studies.The observed result indicated that the formulation containing banana powder gave superior results in terms of wetting time,water absorption, disintegration time, dispersion time and dissolution in comparison to sodium starch glycolate and cross carmellose sodium.It was concluded that banana powder is having excellent super disintegrant property which can very well utilized for developing oro-dispersible tablets.

KEY WORDS: Oro-dispersible tablets, Diltiazem hydrochloride, Banana powder, Sodium starch glycolate,Cross carmellose sodium.

I. INTRODUCTION

Oro dispersible tablets are also called as ODTs, Quick disintegrating tablets, fast dissolving tablets and rapimelts[1]. USFDA defined Oro-dispersible tablets as a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly within matter of seconds when placed upon the tongue.

It has been reported that Dysphagia[2] is common among all age groups and more specific pediatric, geriarticpopulation along with institutionalized patients and patients with nausea, vomiting and motion sickness[3]. Oro-dispersible tablets offer all advantages for solid dosage forms and liquid dosage forms along with special advantages, which include

1.As Oro-dispersible are unit dosage forms, they provide good stability, accurate dosing easy manufacturing, and small packaging size and easy to handle by patients[4,5].

2.No risk of obstruction of dosage form, which is beneficial for travelling patients who do not have access to water.

3. Easy to administer for pediatric, geriatric ad institutionalized patients (especially for mentally retarded and psychiatric patients)

4. Rapid disintegration of tablets results in quick dissolution and rapid absorption which provide rapid onset of action[6].

5. Pre gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increases the bioavailability.[7]

Various processes are employed in formulating oro-dispersible tablets include freeze drying, cotton candy process, moulding, spray drying and mass extrusion and conventional compression.In formulating Oro dispersible tablets

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one of the importantcomponent is super disinegrants. Several excipients are investigated for rapid disintegration of ODTs. A few of them are Crosspovidone, cross carmellose sodium, Sodium starch glycolate, Sodium alginate, Acrylic acid derivatives etc. Evaluation studies of ODTs include hardness test, friability, wetting time, water absorption ratio, moisture uptake studies, disintegration time, dispersion time and dissolution studies. With the pharmacist counseling, intervention and assistance about ODTs, all patients receiving this novel dosage form could be more properly and effectively treated with greater convenience.

II. MATERIALS AND METHODS

List of Chemicals used

1.Diltiazem hydrochloride- Apex Laboatories Chennai
2. Cross carmellose sodium - Colorcon, Goa
3. Sodium starch glycolate - Colorcon, Goa
4. Banana powder - Self made
5. Sodium hydroxide - S.D fine chemicals, Chennai
6. Pottasium dihydrogen phosphate - S.D fine chemicals, Chennai

List of Equipments used

1.Rotary tablet punching machine - Cadmach,Ahmedabad
2. UV –Visible spectrophotometer - Shimadzu, Japan
3. Disintegration Apparatus - Tab Machines
4. Dissolution Apparatus - Electrolab India
5. Digital Weight scale - Anamed
6. Bulk Density Apparatus - Thermonik, Campbell
7. Tablet hardness tester - Tablet tester, Campbell
8. Friabilator - Roche friabilator

III. METHODOLOGY

1. Determination of ʎ max of Diltiazem hydrochloride

Standard stock solution was prepared by dissolving 100mg of Diltiazem hydrochloride in small amount of phosphate buffer(pH 7.4)and the final volume was adjusted to 100ml with phosphate buffer to get stock solutions containing 1000µg/ml. By appropriate dilution standard drug solutions, solutions containing 10µg/ml of Diltiazem were scanned in the range of 200-400nm to determine the wavelength of maximum absorption.

2. Calibration curve of Diltiazem hydrochloride

Standard stock solution containing diltiazem hydrochloride was prepared by dissolving 100mg of Diltiazem in small amount of Phosphate buffer (pH 7.4) and the final volume is adjusted to 100ml.By appropriate dilution of standard drug solutions, solutions containing 1 to 5 Mg/ml were prepared and absorbances were measured by UV visible spectrophotometer at 237nm.

3. Formulation of Dispersible tablet

Oro dispersible tablets containing 30mg of Diltiazem Hydrochloride were prepared using super disintegrants; cross carmellosesodium,sodium starch glycolate and banana powder by direct compression technique according to the formulae given in Table 1

Ingredients	**B1**	**B2**	**S1**	**S2**	**C1**	**C2**
Diltiazem Hcl (mg)	30	30	30	30	30	30
Banana powder(mg)	10	20	--	--	--	--
SSG (mg)	--	--	10	20	--	--
CCS (mg)	--	--	--	--	10	20
MCC (mg)	114	104	114	104	114	104
Mannitol (mg)	30	30	30	30	30	30
Aspartame (mg)	10	10	10	10	10	10
Talc (mg)	3	3	3	3	3	3

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MagnesiumStearate (mg)	3	3	3	3	3	3

Table 1: Formulae used for the preparation of Orodispersible tablet

4. Precompression studies of the powder blend

Prior to the development of a new dosage form with drug, It is essential to determine a few precompression parameters such as

Bulk density[8]

Powder blend equivalent to 10g was accurately weighed and filled in 100ml graduated cylinder and the powder was leveled and the unsettled volume, Vo was noted

The bulk density was calculated in g/cm^3

Bulk density = M/V0

M= mass of granules taken

V0 = apparent volume

Tapped density[8]

Powder blend equivalent to 10g was filled in100ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tester 500 times and tapped volume was noted

Tapped density was calculated in g/cm^3 by the formula

Tapped density = M/V1

M= mass of the granules taken

V1 = Tapped volume

Compressibility Index[8]

The bulk density and tapped density was measured and compressibility index was calculated using the formula

C.I. = { (β_t- β_0) /βt} ×100

Where β_t =tapped density

β_0 = bulk density

Hausners ratio[8]

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula.

Hausner's ratio = **β_t/ β_0**

Where β_t =tapped density

β_0 = bulk density

Assay of blend

The powder blend equivalent to 100mg Diltiazem and dissolved in pH 7.4 phosphate buffer and made up to volume. Then filter the solution through whatmann filter paper and 1ml of resultant solution and dilute to 100ml with phosphate buffer (p^H 7.4) and measured absorbance at 237nm by UV spectrophotometer.

5. Compression of dispersible tablet

The powder blend was mixed properly with glidant talc and magnesium stearate and mixed well. The blended mass then compressed in Cadmach 12 station rotary punching machine. The punched tablets weighed about 200mg(± 7.5mg) and measured about 8.5mm in diameter.

6. Evaluation of Tablet

Evaluation studies of tablet such as Hardness, Friability, Weight variation test, Assay of tablet, Water absorption studies, Wetting time, In vitro dispersion time, Disintegration test, Invitro dissolution n and stability studies were performed.

Hardness[9]

Tablet hardness has been defined as the force required for breaking a tablet in a diametric compression test. A tablet was placed between two anvils of the hardness tester (Tablet tester, Campbell,Mumbai) force was applied to the anvils, and the crushing strength that is required to break was recorded.

Friability[9]

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. Pre-weighed tablet samples (20 tablets)were placed in the friabilator, which was then operated for 100 revolutions, dropping the tablets at a distance of 6 inches with each revolution.The percentage friability was calculated using the formula.

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

Weight variation test[10]

2o tablets were selected at random and weighed individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablets weighed around 200mg, I.P. specifies that the tablet pass the test if not more than two of the individual weights deviate from the average weight by more than 7.5%.

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Assay of tablet[11]

Ten tablets were randomly weighed and a weight equivalent to 100mg of Diltiazem was taken and dissolved in 100ml of pH 7.4 phosphate buffer. One ml of the resultant solution was diluted to 100ml with phosphate buffer and filtered. The filtered solution was measured for its absorbance using UV spectrophotometer at 237nm.

Water absorption method

Water absorption method was conducted as per the method reported by Sunil Kumar Battu et al.[12] The tissue paper was placed in a petri dish of 10cm diameter. Methylene blue, a water-soluble dye was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petri dish. The time required for water to reach the upper surface of the tablet and to wet them completely was taken as the wetting time. The weight of the tablet prior to placement in petri dish was noted (w_b), the wetted tablet was removed and reweighed(w_a), water absorption ratio R was then determined according to the following equation.

$$R = w_a - w_b / w_b \times 100$$

Wetting time

Wetting time was measured by placing a tablet on a piece of tissue paper folded twice in a small petri dish containing 6ml of methylene blue solution and measuring the time required for complete wetting of the tablet which can be identified by the movement of the dye colour on the surface of the tablet.

In vitro dispersion time[13]

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of p^H 7.4 phosphate buffer. Three tablets from each formulation were randomly selected and in vitro dispersion time was noted and expressed in seconds.

Disintegration test

The disintegration time of the prepared tablets were found out by using disintegration apparatus.6 tablets were placed inside the tube and the test was conducted in distilled water maintained at 37^0C. The time at which all the tablets disintegrate and pass through the mesh completely was noted as disintegration time.

In Vitro Dissolution

Diltiazem release from different formulations was determined using a USP XIX paddle apparatus 2 under sink condition. The dissolution medium was 900ml phosphate buffer (p^H 7.4) at 37±0.2^{0}C with paddle speed of 50 rpm., to simulate in vitro conditions. All experiments in triplicate and average values are were taken. The formulation prepared was subjected to dissolution tests for 30min. Samples(10ml)were withdrawn at predetermined intervals, filtered through whatmann filter paper and replaced by anequal volume of dissolution medium. Drug content in the sample was determined by measuring the absorbance using UV visible spectrophotometer at 237nm.

Stability studies

The prepared formulations which showed best result in vitro was selected and kept for stability testing for a period of one month. The tablets were kept at 40±2^{0}C/75%±5% RH in a stability chamber and samples were withdrawn at 0 and 30th day and evaluated for drug content, dissolution and disintegration time.

IV. RESULTS AND DISCUSSION

Calibration data for Diltiazem hydrochloride

Concentration (µg/ml)	Absorbance
1	0.0583
2	0.1163
3	0.1835
4	0.2554
5	0.3001

Table 2: calibration data of diltiazem hydrochloride

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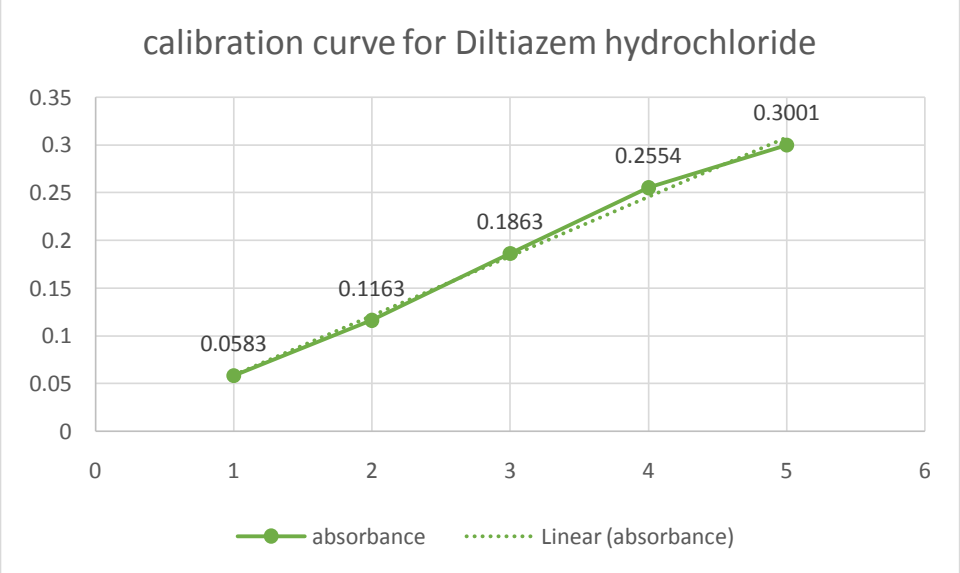

Figure 1: calibration curve for Diltiazem hydrochloride

A calibration curve for Diltiazem hydrochloride was constructed atp^{H}7.4 phosphate buffer by scanning the diluted drug solution at 237nm using UV visible spectrophotometer. The linearity of the calibration curve was found to be in the range of 1-5 µg/ml.

PRECOMPRESSION EVALUATION OF POWDER BLEND

All the formulations were prepared under similar conditions to avoid process variables. The powder blend showed an angle of repose of less than 30, which reveals good flow property. The loose bulk density and tapped bulk density for all the formulation blends varied from 0.349gm/cm^3 to 0.452 gm/cm^3 and 0.404gm/cm^{3}to 0.532gm/cm^3 respectively (table 5). The result of Carr's consolidation index or (%) compressibility index for the entire formulation blend ranged from 12 to 20 indicating excellent compressibility index. The physical properties of blend prepared with banana powder showed better results than that of the blends prepared with CCS and SSG. This clearly demonstrated the efficiency of banana powder as pharmaceutical excipient.

Property	B1	B2	S1	S2	C1	C2
Angle of repose	27.24 ±0.65	27.34±0.47	26.01±0.32	27.42±0.44	24.12±0.12	22.23±0.24
Bulk density	0.432±0.45	0.422±0.36	0.420±0.15	0.414±0.32	0.359±0.22	0.452±0.35
Tapped density	0.515±0.51	0.502±0.22	0.500±0.24	0.518±0.39	0.424±0.12	0.516±0.42
% Compressibility	16.0±0.19	16.0±0.23	16.0±0.31	20.0±0.37	15.3±0.12	12.0±0.38
Hausners ratio	1.190±0.18	1.903±0.12	1.904±0.12	1.250±0.17	1.181±0.12	1.141±0.20

Table 3: Precompression properties of tablet blend (n=3, S.D)

EVALUATION OF TABLETS

The hardness values ranged from 3.0 to 3.8 kg/cm^3 for all formulations (Table 3). The entire tablets passesweight variation test as the average % weight variation was within in the pharmacopeiallimit of 7.5%. It was found to be 197.1±0.70mg to 200.2 ±0.45mg. The weight of all the tablets were found to be uniform with low standard deviation (Table 3). The friability values were found to be within the limit (0.1- 0.9%). The drug content of Diltiazem hydrochloride determined at 237nm ranges from 97.19 to 100.12% and complies with IP standard.

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Parameter	B1	B2	S1	S2	C1	C2
Hardness (kg/cm^2)	3.2±0.34	3.5±0.19	3.8±0.22	3.0±0.14	3.2±0.12	3.5±0.14
Weight variation(mg)	199.1±0.70	200±0.25	198.2±0.13	199.9±0.50	199.4±0.25	199.1±0.40
%Friability(%)	0.407	0.309	0.551	0.85	0.702	0.527
Drug content	99.62	97.87	98.34	98.79	99.41	100.12
Wetting time(sec)	13.00±1.06	12.1±1.52	16.40±1.24	18.40±1.12	16.10±1.36	14.20±1.02
Water absorption	1.57	1.89	1.35	1.24	1.40	1.46
Invitro dispersion(sec)	15	12	24	35	21	19
Disintegration time (sec)	34.4	31.5	52.5	54.6	39.5	37.4

Table 4: Evaluation of tablet

Wetting time is closely related to the inner structure of tablet. This experiment mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet and subsequent wetting of tablet. This shows the wetting process was very rapid in almost all formulations. This may be due to the ability of swelling followed by breaking and capacity water absorption. It was found to be in the range of 12.04s to 18.42 s. Water absorption ratio which is important criteria for understanding the capacity of disintegrants to swell in the presence of little amount of water, was calculated. The tablet showed values in the range of1.24 to 1.89(Table 6) This shows all the formulations has good water absorption capacity.

The use of disintegrants for preparing ODTs highly effective and commercially feasible. These superdisintagrants accelerate disintegration of tablets by virtue of their ability to absorb large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well.

In this study, banana powder was employed as super disintegrant and its effect was compared with CCS and SSG which are two commonly employed superdisintegrants. Formulations containing banana powder as super disintegrant showed better results in comparison with CCS and SSG. In the wetting studies, the formulation B1 and B2 containing 5 and 10% banana powder showed a wetting time of about 13 and 12.1s. similarly formulations S1,S2 C1 and C2 containing SSG and CCS showed a wetting time of 18.4, 16.4, 16.1 and 14.4 respectively. Similarly in the water absorption studies formulation containing 5% super disintegrants gave values of 1.57,1.37 and 1.40 for banana powder, CCS and SSG respectively. On the other hand formulations containing 10% super disintegrants gave a value of 1.89, 1.24 and 1.46 respectively for banana powder, CCS and SSG. From the observed results it was found that the formulations containing banana powder gave superior results than CCS and SSG.Also, it was noted that 10% concentration gave better results for banana powder and CCS, where as 5% concentrations gave good results for SSG.

The most important parameter that needs to be optimized in the development of ODTs is the disintegration time of tablets. In the present study all the tablets disintegrated with in 55s fulfilling the official requirements (>3min) for dispersible tablets.[14]Table 6 gives the disintegration time achieved by all formulations. Disintegration time for tablets prepared with banana powder (B1 and B2) was faster than the CCS (C1and C2)and SSG (S1 and S2) formulations. Increase in disintegrant concentration resulted in faster disintegration time for bananapowder and CCS whereas slower disintegration time was achieved with increase in concentration for SSG. This may be due to the formation of viscous gel layer by SSG which might have formed a thick barrier to further penetration of the disintegration medium and hindered the disintegration and leakage of tablet contents. Thus, it was observed that disintegration was retarded with higher concentration of SSG. The faster disintegration of banana powder and CCS can be attributed to their rapid capillary activity and pronounced by hydration with little tendency to gel

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formation[15]. These results are in consistent with wetting and water absorption studies.

TIME IN MIN	PERCENTAGE DRUG RELEASED					
	B1	B2	S1	S2	C1	C2
5	71.8	86.92	72.22	43.02	68.35	83.2
10	79.8	89.2	84.10	53.01	70.15	89.27
15	83.6	95.3	84.10	65.91	74.31	91.15
20	85.5	98.1	86.45	70.94	77.8	92.00
25	88.3	99.6	86.92	71.41	83.55	94.35
30	92.28	101.95	90.21	75.64	89.12	100.4

Table 5: Dissolution studies

The dissolution process of tablet depends upon the wetting followed by the disintegration of the tablet.The influence of super disintegrants on the dissolution of the Diltiazem is given in Table .It was observed that the tablets containing banana powder and CCS as super disintegrants exhibited a higher percentage release in comparison with tablets containing SSG. The rapid increase in dissolution of Diltiazem may be attributed to rapid swelling and disintegration of tablet in to apparently primary particles, while tablets prepared with SSG disintegrate by rapid uptake of water followed by rapid and enormous swelling in to primary particle but more slowly due to the formation of a highly viscous gel layer.

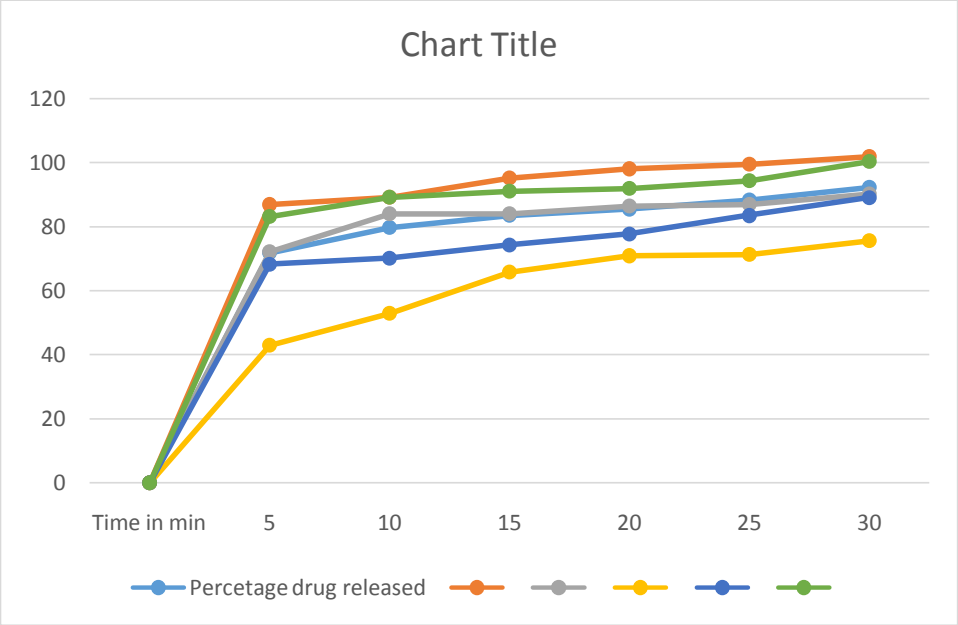

Figure 2: Dissolution profile of formulations

Banana powder and CCS exhibits higher capillary activity and pronounced hydration with a little tendency to form a viscous gel layer. In regards to the effect of concentration of the super disintegrants on the dissolution rate of the drug, Banana powder and CCS showed an increase in the total drug released with increase in concentration from 5% to 10% where as a decrease in the dissolution was observed with SSG. These results were consistent with the reports obtained from the disintegration, wetting and water absorption studies. The stability studies indicated no significant reduction in drug content, dissolution and disintegration rate. Hence the prepared tablets are very much stale at accelerated stability conditions.

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Parameter	B2		S2		C2	
	0 DAYS	30 DAYS	0 DAYS	30 DAYS	0 DAYS	30 DAYS
Drug content (%)	99.62	99.15	98.34	97.35	100.12	99.5
Drug release (%)	98.3	95.12	87.4	86.5	92.5	89.35
Disintegration (%)	31.5	29	52.5	48.5	37.4	37

Table 6: stability studies of selected formulations

V. SUMMARY

The present study was aimed at evaluating a natural disintegrant, banana powder for preparing oro dispersible tablets and comparing its effect with other synthetic super disintegrants like sodium starch glycolate and croscarmellose sodium. Six formulations were made using different concentrations (5% and 10%) of three superdisintegrants. The powder blend prepared for compression was evaluated for precompression parameters like bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose. The results obtained indicated that all the powder blends were having good properties for preparing the tablets by direct compression technique.

Tablets were preparedby direct compression using rotary tablet punching machine to a target average weight of 200mg. The prepared tablets were evaluated for various post compression parameters like hardness, weight variation, friability, disintegration and dissolution test. The tablets were also subjected to wetting studies, water absorption studies and invitro dispersion studies. The observed results indicated that the formulation containing banana powder gave superior results in terms of wetting time, water absorption, disintegration time, dispersion time and dissolution in comparison to sodium starch glycolate and croscarmallose sodium. The optimum concentration for the super disintegrant was found to be 10% for banana powder and CCS where as it was 5% for SSG.

Formulation B2 containing 10% banana powder showed the fastest disintegration time of 31.5s and highest percentage drug release of 101.95 within 30 minutes and hence it was selected as the best formulation of all the six formulations prepared. Among the formulations containing CCS and SSG, formulation C2 and S1 were found to be best ones with disintegration times of 37.4 and 52.5s respectively and percentage drug release of 100.4 and 90.21 for C2 and S1 respectively.

Stability studies indicated that the prepared formulations were stable at accelerated stability conditions and there was no significant reduction in the dug content, disintegration rate or dissolution rate.

VI. CONCLUSION

The present study was aimed at evaluating the disintegration property of banana powder and comparing it with other synthetic superdisintegrants in the preparation of ODTs. It was concluded that banana powder is having excellent superdisintegrant property which can be very well utilized for developing ODTs. Banana powder is cost effective than other commonly used binders, diluents and disintegrants. More over banana powder is a"Natural additive" with nutritional values. Thus, banana powder can be used as a natura disintegrant in the formulation and development of ODTs and other patient friendly dosage forms.

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