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Formulation and *In-Vitro* Evaluation of Fast Dissolving Tablets of Clopidogrel Contaning Natural Superdisintegrants

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ABSTRACT

The present study was carried out to develop fast dissolving tablets of Clopidogrel. Banana Powder, Isapgol Mucilage and Sodium Starch glycolate were used as Superdisintegrants and use Crospovidone 5mg in all formulations. Clopidogrel is used to treat heart attack and strokes in persons with heart disease (recent heart attack). It helps to keep blood flowing smoothly in your body. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The tablets were prepared by direct compression method. The prepared tablets were shown good compression parameters like weight variation wetting time, water absorption ratio, hardness, friability. All tablet formulations showed quick disintegration time, which is very characteristic of fast dissolving tablets. All the formulations showed rapid percentage drug release (58.51% - 99.64 %)). The rapid drug disintegration (17 sec) was noticed in F8 formulation when compare to other formulation. Among all the formulations F8 (contain sodium starch glycolate) showed maximum % drug release in 30 min hence it is considered as optimized formulation.

Keywords: Banana Powder, Clopidogrel, Fast dissolving tablets, Isapghol Mucilage, and Sodium Starch glycolate.

INTRODUCTION

Tablets may be defined as the solid unit dosage form of medicament or medicaments with or without suitable diluents and prepared by compression. It comprises a mixture of active substance and excipients, usually in powder form, pressed or compacted form a powder into a solid dose. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [1].

For the treatment or management of diseases, oral delivery is giving much more attention from the ancient decade. A new concept in oral delivery is mouth dissolving tablets (MDT) are widely accepted nowadays. MDT are solid dosage forms which, when placed in the mouth, disintegrate dissolve and release active agents within a few minutes without need for water. It has more significance to geriatrics, pediatrics and bedridden patients because they have a problem in swallowing and the patients with Dysphasia [2].

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally

less than 60 seconds. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage forms known as orally disintegrating (dispersible) tablets (ODTs) or Fast disintegrating (dissolving) tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets (MDTs), immediate release tablets which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water[3].

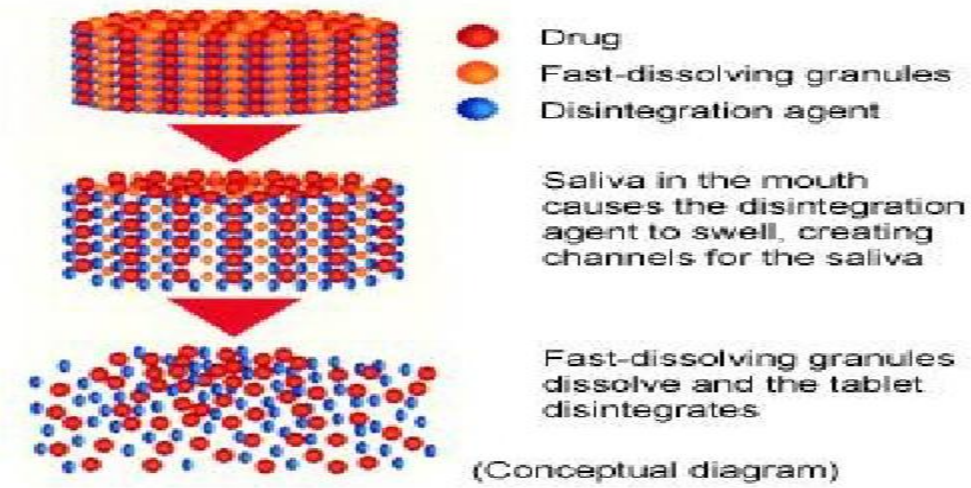

Fig.1: Schematic diagram of Mechanism of fast dissolving tablet

Advantages of fast dissolving tablets

- No need of water to swallow the tablet.
- FDTs can be easily administered to paediatric, elderly and mentally disabled patients.
- Accurate dosing as compared to liquids.
- Dissolution and absorption of the drug is fast, offering rapid onset of action.
- Bioavailability of drugs is increased10as some drugs are absorbed from mouth, pharynx and oesophagus through saliva passing down into the stomach.
- Advantageous over liquid medication in terms of administration as well as transportation.
- First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
- Offering improved safety [4].

Clopidogrel is used to treat heart attack and strokes in persons with heart disease (recent heart attack). It helps keep blood flowing smoothly in your body. It is having half life 6hrs and t_{max} is 1.4 hrs. It is taken by mouth; Onset of action is about 2 hours and lasts for five days [5].

The aim and objective of research work is to formulate and evaluate Clopidogrel fast dissolving tablets by using natural superdisintegrants like Banana powder and Isapghol mucilage and artificial superdisintegrants like sodium starch glycolate, study the different concentration of superdisintegrants in drug release when compared with natural and artificial superdisintegrants.

MATERIALS AND METHODS

Material

Clopidogrel was gifted from Aurabindo pharma Hyderabad, India. Banana powder and Isapghol mucilage procured from Merck specialties and Sodium Starch Glycolate, Coss povidone, sodium saccharine, Mannitol, Talc, Magnesium Stearate and Mint was used as pharmaceutical ingredients were obtained from Zydus cadila healthcare Ltd. India. The Distilled water was used obtained from Water purification unit.

Preparation of fast dissolving tablets of Clopidogrel

In present investigation fast dissolving tablets of Clopidogrel were prepared by direct compression using different superdisintegrant. For this Clopidogrel and all other excipients according to the formula were weighed accurately. Clopidogrel, Mannitol (Pearlitol SD 200), preoared banana powder and Isabghol mucilage Sodium Starch Glycolate, Cross povidone, Mint and sodium saccharine were passed through sieve # 40. All the above sieved ingredients were then mixed for 15 minutes. Magnesium stearate and Talc previously passed through sieve # 60 was then mixed with above blend for 5

minutes and add cross povidone. The mixture(s) was then allowed to compress using 16 station rotary tablet compression machines with 8.0 mm flat round punches with tablet weight 200 mg [6].

Table 1: Formulation table showing various compositions

Ingredients (mg)	F1	F2	F3	F4	F5	F5	F7	F8	F9
Clopidogrel	75	75	75	75	75	75	75	75	75
Banana Powder	2	4	6	-	-	-	-	-	-
Isapgol Mucilage	-	-	-	2	4	6	-	-	-
Sodium Starch glycolate	-	-	-	-	-	-	2	4	6
Cross povidone	5	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1	1	1
Sodium saccharin	2	2	2	2	2	2	2	2	2
Mannitol	112	110	108	112	110	108	112	110	108
Mint flavor	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total Weight (mg)	200	200	200	200	200	200	200	200	200

Selection of wavelength for analysis of Clopidogrel: Accurately measured 1.0 ml of standard stock II solution was transferred into 10 ml volumetric flask and diluted to 10 ml to give concentration of 10 µg/ml and it was used for initial spectral scan in the UV range of 200-400 nm to detect maximum wavelength and further dilutions for linearity were prepared from the stock solution by allegation method [7]. The λ_{max} was found to be 290 nm

Standard calibration curve of Clopidogrel in pH 6.8 phosphate buffer solution
100 mg of **Clopedogrel** was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 2,4,6,8 and 10µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}) i.e., 290 nm [8].

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm^{-1} and 550 cm^{-1}.

Micromeritics properties
Flow properties of all batches were evaluated by measuring the angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner's ratio [9].

Post-compression evaluation parameters of fast Dissolving tablets of Clopidogrel
Weight variation test. I.P. procedure for uniformity of weight was followed. Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight [10].

Weight variation (%) = [(average weight – individual weight)/average weight] × 100 Hardness testing. The hardness of the tablets was determined by diametric compression using Monsanto hardness tester. A tablet hardness of about 3- 4 kg/cm^2 is considered adequate for mechanical stability [11].

Thickness. Ten Tablets were selected randomly from individual formulations and thickness was measured by using Verniar calliper scale, which permits accurate measurement [12].

Friability test. The friability of the tablets was measured in a Roche Friabilator. Compressed tablets that loose less than 0.5% to 1.0% in weight are generally considered acceptable. Ten tablets were weighed (initial weight) and then transfer into Roche Friabilator. It was subjected to 100 revolutions in 4 min. The tablets were dedusted and reweighed (final weight).

These two weights were applied to following formula and friability was calculated. The weight loss should not be more than 1% [13].

RESULTS AND DISCUSSION

Determination of absorption maximum of Clopidogrel

From the UV Spectrophotometric analysis, it was conclude that the drug, Clopidogrel showed a λ_{max} at 290 nm. Therefore the observed λ_{max} was used for further work to analyze the test sample.

Standards graph of Clopidogrel in PH 6.8 phosphate buffer

The solution obeyed Beer's Lambert's law over a concentration range of 2-10 µg/ml with a regression co-efficient of 0.995. This standard curve was used further to estimate Clopidogrel in the *in vitro* studies. The absorbance measures at 290 nm in UV Spectrophotometer against reagent blank with simulated saliva pH 6.8 PBS.

Table 2: Data of standard calibration curve of Clopidogrel in pH 6.8 PBS

Sl. No	Concentration (µg/ml)	Absorbance (290 nm)
0	0	0
1	2	0.264
2	4	0.416
3	6	0.636
4	8	0.864
5	10	1.048

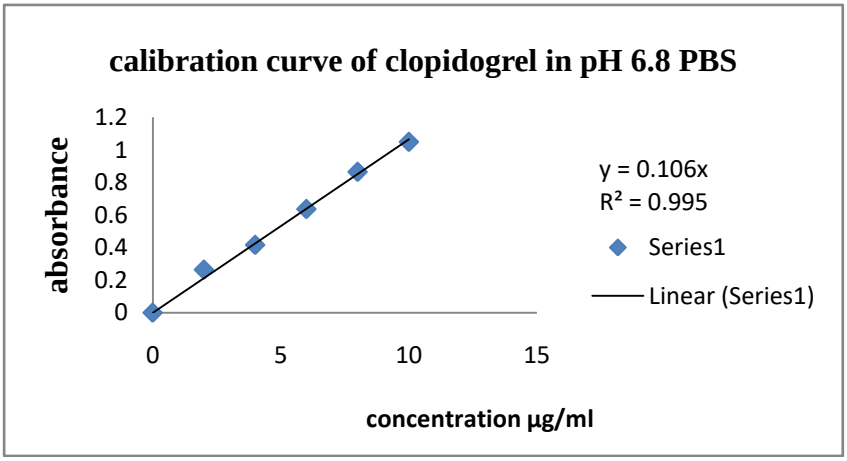

Fig.2: Standard Calibration curve of Clopidogrel in pH 6.8 phosphate buffer

Table 3: Evaluation of pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	23.19	0.52	0.66	10.34	1.11
F2	24.10	0.5	0.62	13.79	1.16
F3	24.77	0.5	0.6	20	1.25
F4	25.27	0.58	0.625	10.77	1.07
F5	25.17	0.43	0.52	17.33	1.21
F6	26.56	0.47	0.57	17.48	1.21
F7	29.09	0.48	0.54	12.01	1.13
F8	29.74	0.42	0.49	12.40	1.14
F9	29.93	0.361	0.40	11.59	1.13

Micromeritic properties

Flow properties of batches were evaluated by measuring the angle of repose and compressibility index. In the evaluation of flowability of dry solid ,the substances shows excellent flowability of performance, when the angle of repose have the value found to in between 23.19^0 to $29.93^{0'}$while when compressibility index has value below 10.22 %, Hausner's ratio was below 1.24, no aid is needed for enhancing the flowability of power. Thus, angle of repose and compressibility index are indicates of good flowability of power blend, showing no need for addition of glidant to enhance flowability. The better flows properties of power blend indicate that the mixture of powder produced were non-aggregated. The micromeritic properties of powder blend is shown in table 3.

Table 4: Evaluation of post compression parameters of Clopidogrel Fast dissolving tablets

Formulation codes	Average weight(mg)	Hardness (kg/cm^2	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	97.5	2.2	0.56	3.9	98.66
F2	98.02	2.1	0.52	3.8	99.12
F3	94.21	2.6	0.59	3.7	99.24
F4	96.59	2.4	0.55	3.8	99.69
F5	98.89	3.8	0.52	3.9	98.64
F6	97.93	3.5	0.49	3.7	97.86
F7	99.06	3.7	0.53	3.5	99.62
F8	**98.82**	**3.8**	**0.58**	**3.6**	**99.85**
F9	97.36	2.9	0.43	4.4	98.92

Table 5: Wetting time, Water absorption ratio and *in vitro* disintegration time

Formulation code	Wetting time (sec)	Water absorption ratio	*In-vitro* disintegration time
F1	16	20	30
F2	15	30	29
F3	12	40	28
F4	18	30	31
F5	16	20	30
F6	12	40	29
F7	14	30	25
F8	**11**	**50**	**17**
F9	12	40	18

Wetting Time. Wetting time is closely related to the inner structure of the tablet, these are less wetting time for batch F8. Due to it contain sodium starch glycolate. But formulations containing banana powder and isapghol mucilage somewhat high wetting time than that of formulation containing sodium starch glycolate. The results of wetting time are shown in table 5.

***In vitro* disintegration time:** *In vitro* disintegration studies showed from 3.3-4.6 minutes. The F8 formulation showed very less in vitro disintegration time i.e. 17 Sec.

Water absorption ratio:

Water absorption ratio which is important criteria for understanding the capacity of disintegrates to swell in presence of little amount of water, was calculated. It was found to be in the range of 10 – 50 % seconds. The values of water absorption ratio shown in table

The formulation prepared by direct compression method formulation containing individual superdisintegrants shows lower water absorption ratio when compare to formulation containing sodium starch glycolate .The water absorption ratio also decreases due to less swelling property. The formulation prepared by direct compression method formulation containing individual super disintegrants sodium starch glycolate shows higher absorption ratio when compared to formulation containing banana powder and Isapghol mucilage these super disintegrants have less swelling property.

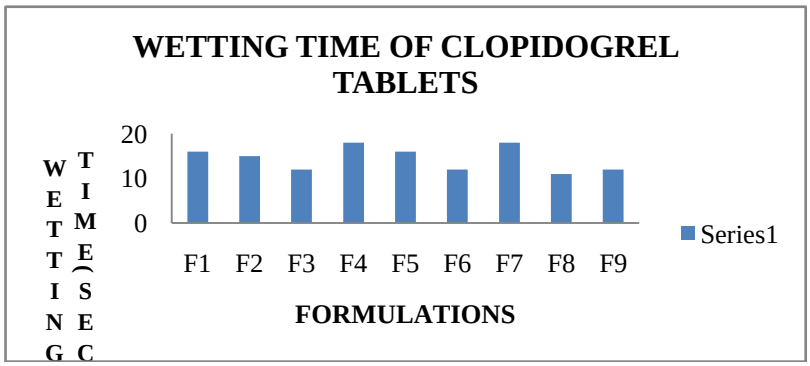

Fig.3:Wetting time of Clopidogrel tablets

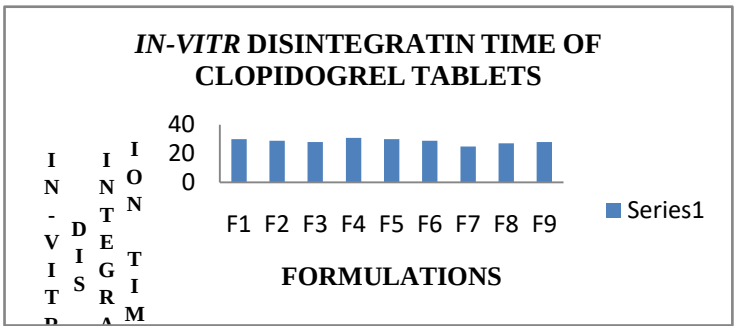

Fig.4:*In vitro* disintegration time of Clopidogrel tablets

Table 6: Dissolution data of Clopidogrel

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	**0**	0
5	58.26	60.08	64.18	54.43	54.42	49.89	54.77	**58.51**	42.6
10	66.46	69.39	69.95	65.29	62.87	59.76	66.84	**65.65**	59.36
15	78.87	75.82	75.19	79.55	69.93	68.01	73.46	**76.46**	69.82
20	84.17	89.21	80.23	89.25	76.86	71.65	79.69	**85.29**	82.98
30	92.49	95.52	98.79	98.59	95.87	94.69	89.61	**99.64**	95.36

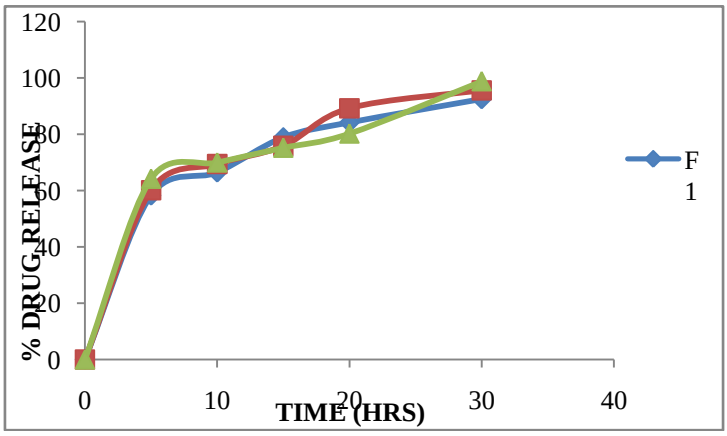

Fig.5: Dissolution profile of formulations F1, F2, F3

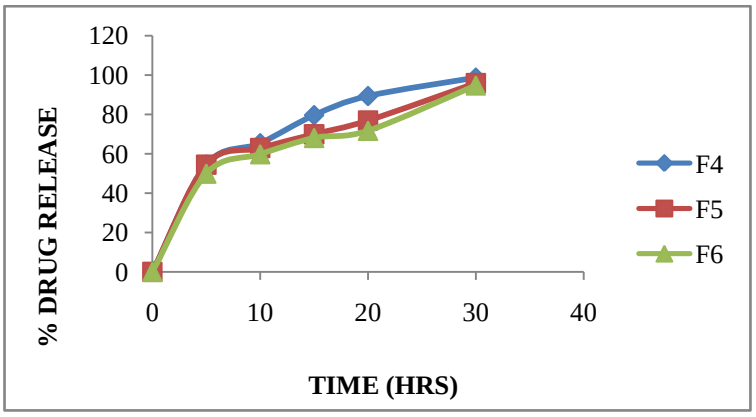

Fig.6: Dissolution profile of formulations F4, F5, F6

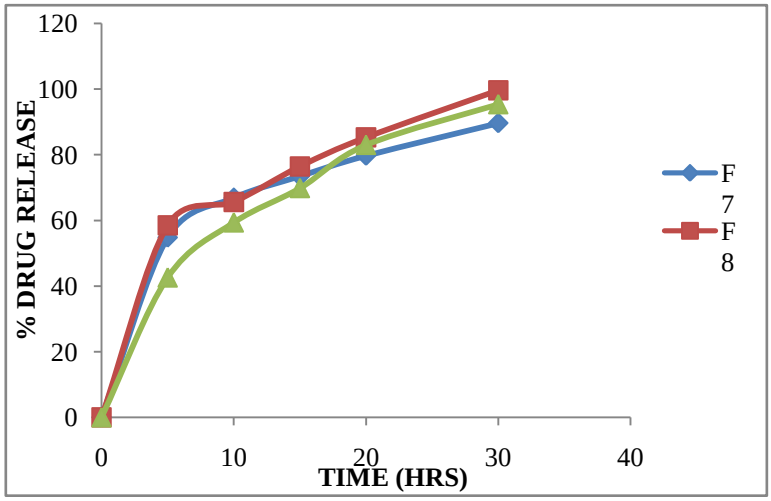

Fig.7: Dissolution profile of formulations F7, F8, F9

***In vitro* drug release study**

All the formulations were subject for *in vitro* dissolution studies tablets dissolution tester USP XXIII. The dissolution medium PH 6.8 PBS were used to study the drug release. The samples were withdrawn at different intervals of time and analyzed at 290 nm using UV spectrophotometer. Percentage drug release was calculated on the basis of average amount of Clopidogrel present in the respective formulation. From the table it was evident that the formulation prepared with Banana Powder were showed good drug release i.e., F3 formulation (98.79%) in higher concentration of Blend i.e 6 mg. Formulations prepared with Isapghol Mucilage showed good drug release i.e., 98.59% (F4 formulation) in 2 mg concentration. Formulations prepared with Sodium Starch glycolate showed maximum drug release i.e., 99.64% (F8 formulation) at 30 min in 25 mg of blend. Among all formulations F8 considered as optrimised formulation which showed maximum drug release at 30 min i.e., 99.64%. Finally concluded that F8 formulation contains Sodium Starch glycolate was optimized formulation.

CONCLUSION

In present studies, it may be conclude that the fast dissolving tablets of Clopidogrel can be prepared by direct compression using different superdisintegrants. The formulations prepared with Banana Powder were showed good drug release i.e., 98.79 (F3) in higher concentration of blend i.e., 6 mg. Formulations prepared with Isapgol Mucilage showed good drug release i.e., 98.59% (F4) in 2mg concentration. Formulations prepared with Sodium Starch glycolate showed maximum drug release i.e., 99.64 % (F8). This formulation showed the least disintegration time of 17 sec and the highest release of more than 99.64% of drug in 30 min. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the patient compliance and the absorption leading to its increased bioavailability. Direct compression technique would be an effective and simple alternative approach compared with the use of more expensive process and adjuvant in the formulation of fast dissolving tablets. From the characterization of oral dispersible tablets of Clopidogrel it can be

concluded that formulation containing sodium starch glycolate is optimized formulation. From this data natural super disintegrants like banana powder and isapghol mucilage also showed good super disintegration action when compare with artificial superdisintegrants.

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