FORMULATION AND EVALUATION OF CLOPIDOGREL BISUFATE IMMEDIATE RELEASE TABLETS BY USING NATURAL GUMS

Dr. D. Hema naga durga[1], Ch. Ashwini[2], C. Varsha[3], D. Chiranjeevi[4], Ch. Sahana Reddy[5], Ch. Swetha[6]

Department of Pharmaceutical Technology, Malla Reddy College of Pharmacy, Hyderabad-500100

ABSTRACT

Clopidogrel bisulfate is an antiplatelet drug used mainly to prevent heart attack and stroke. The aim of this study was to formulate and evaluate immediate release tablets of clopidogrel bisulfate using natural gums by the direct compression method. Natural polymers such as gum tragacanth and guar gum were used as disintegrants. Six formulations (F1–F6) were prepared and evaluated for precompression parameters like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio, which showed good flow properties and postcompression evaluation included hardness, thickness, weight variation, friability, disintegration time and *in-vitro* dissolution studies. All formulations met pharmacopeial limits with disintegration times ranging from 2 to 4 minutes and rapid drug release in acidic medium (0.1N HCl) in 30 mins. Formulations F_2 and F_4 showed faster disintegration and good dissolution profiles which are compared with marketed formulation clopitab. The study concludes that natural gums are effective, economical and safe disintegrants for immediate release tablets and they can improve tablet performance and patient compliance.

Keywords: Clopidogrel bisulfate, guar gum, microcrystalline cellulose, immediate release tablets

INTRODUCTION

INTRODUCTION TO IMMEDIATE RELEASE TABLETS[1]:

Immediate release drug delivery systems are described as immediate release tablets that are manufactured to disintegrate and release the drug without special rate controlling features such as special coatings or alternative technologies, hence the traditional type of drug delivery. It's also a system. Oral administration is one of the most popular routes of administration for systemic effects due to its ease of ingestion, simplicity, safety, convenience, non-invasiveness, versatility, and most importantly, patient compliance. Solid oral administration systems are inexpensive to manufacture because they do not require sterile conditions. An ideal dosage regimen of drug therapy is the one, which immediately nab the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constantly for the entire duration treatment, of late, the scientists have focused their attention

on the formulation immediately released tablet. The effort of developing a rapidly disintegrating tablet is accomplished by using suitable diluents and super disintegrants. Although, increased focus and interest generated in the area of controlled release and targeted drug delivery system in recent years, tablet dosage forms that are intended to be swallowed whole, disintegrate, and release their medicaments fast and furiously in the gastrointestinal tract.

SALIENT FEATURES OF IMMEDIATE RELEASE TABLETS[2]:

1. Drugs should have long biological half-lives for immediate release drug delivery.
2. The drug is released quickly and completely in one shot.
3. High bioavailability expected in an immediate release dosage form.
4. Elimination half-life are also requirements for immediate release drug delivery systems.
5. Pharmacotherapeutic intervention is possible.

EXCIPIENTS COMMONLY USED FOR IMMEDIATE RELEASE PREPARATIONS[3]:

Excipients used in IR tablets contain at least one suspending agent, lubricant, disintegrant, binder, glidant.

Name of excipients	Percentage
Disintegrating agents	0.25-2%
Binder	2-10%
Lubricant	2-10%

Table 1: Name and weight percentage of various excipients

METHODOLOGY

ANALYTICAL METHOD DEVELOPMENT:

CONSTRUCTION OF STANDRAD CURVE OF 0.1N HCl SOULTION[4]:

Preparation of 0.1N HCl:

Prepare 0.1N HCl buffer: 8.5 mL of concentrated HCl transferred in a 200 of distilled water with continuous stirring and make up with distilled water up to in 1000 mL.

Preparation of sample[5]:

Weigh 100 mg drug, dissolve in 20 mL of ethanol. After complete solubility of drug in ethanol add 0.1N HCl make up to 100 mL. It was stock solution I, from this 1 mL was taken and transferred into 100 mL of volumetric flask and make up to 100 mL with 0.1N HCl. It was stock solution II, from this Take 1, 2, 3, 4, 5 mL in 10 mL volumetric flask and make up to mark. These gives 10, 20, 30, 40 and 50µg/mL. Measure absorbance at 272 nm.

FORMULATION DEVELOPMENT:

FORMULATION OF CLOPIDOGREL BISULFATE IMMEDIATE RELEASE TABLETS:

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Clopidogrel	75	75	75	75	75	75
Gum tragacanth	6	12	18	-	-	-
Guar gum	-	-	-	6	12	18
Talc	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Microcrystalline cellulose (q.s)	115	109	103	115	109	103
Total(mg)	200	200	200	200	200	200

Table 2: Formulation table of Clopidogrel bisulfate immediate release tablets

Direct compression method:

Drug (clopidogrel bisulfate) and required excipients (tragacanth, guar gum, magnesium stearate, talc, microcrystalline cellulose) were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a mortar and pestle for 15mins. The obtained blend was lubricated with magnesium stearate and talc was added and mixing was continued for further 5 mins. Now the resultant mixture was manually compressed into tablets by using rotary punching machine. Finally, the tablets were obtained.

Pre compression parameters:

1. **Angle of repose[7]:**

The angle of repose of API powder and ingredients is determined by the funnel method. The accurately weighed powder blend is taken in the funnel. The height of the funnel is adjusted in a way that the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$$\text{Tan } \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

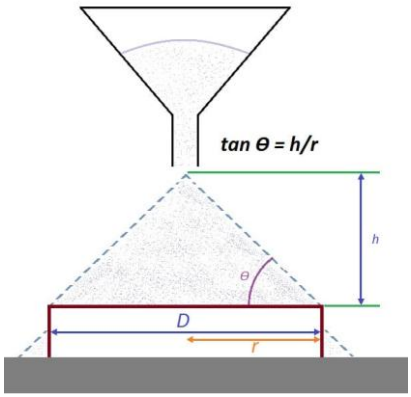

Figure 1: Angle of repose.

2. **Bulk density[8]:**

The powder sample under test is screened through sieve No. 18 and the sample equivalent to 25 gm is weighed and filled in 100 mL graduated cylinder and the powder is levelled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm³ by the formula.

$$\text{Bulk density} = V_0 \times M$$

Where,

V_0 = apparent unstirred volume

M = powder mass

3. **Tapped density[9]:**

The powder sample under test is screened through sieve No. 18 and the weight of the sample equivalent to 25 gm is filled in 100 mL graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tapping is proceeded further for an additional tapping 750 times and tapped volume V_t is noted. The tapped density is calculated in g/cm³ by the formula.

$$\text{Tapped density} = M/V_t$$

Where,

M = weight of sample powder taken

V_t = tapped volume

4. **Compressibility index/carr's index[10]:**

The compressibility index of the powder blend is determined by Carr's index to know the flow character of a powder. This formula for Carr's index is as below:

$$\text{Carr's index (\%)} = [(TD-BD)/TD]x100$$

Where,

TD = Tapped density

BD = Bulk density

5. Hausner's ratio[11]:

Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called Hausner's ratio. It is calculated by the following equation:

H = tapped density/bulk density

POST COMPRSSION PARAMETERS[12-16]:

1. Uniformity of thickness:

Thickness was determined by using vernier callipers and the average thickness was determined in mm. Average of three readings were taken and the results were tabulated.

2. Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of each tablet was determined and the average hardness value was calculated.

Figure 2: Hardness tester

3. Weight variation test:

Twenty tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limits.

4. Fraibility test:

Friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and the weight was noted as initial and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again and the weight was noted as final. For

conventional tablets, the percentage friability should be less than 1%, whereas friability values of up to 4% are acceptable for oral disintegrating and chewable tablets.

$$F(\%) = W_{Initial} (W_{Initial} - W_{Final}) \times 100$$

Figure 3: Friability test apparatus

5. *In-vitro* disintegration test:

The test is carried out on 6 tablets using tablet disintegration apparatus, use 0.1N HCl buffer at 37°C ± 2°C as a disintegration media and measure the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the mesh.

6. *In vitro* dissolution studies[17-22]:

In vitro drug release of the sample was carried out by using USP Dissolution Apparatus II (Paddle Type) at 50 rpm. The dissolution medium, 900 mL of pH 0.1 N HCl buffer, was placed into the dissolution flask maintaining the temperature at 37 ± 0.5°C. One tablet was placed in each flask of dissolution apparatus and apparatus allowed to run. Aliquots of 5 mL of dissolution medium were withdrawn at specific time intervals (5, 10, 15, 20, 25, 30 minutes), filtered and 5 mL of fresh buffer sample was replaced as soon as the drug samples were withdrawn. The amount of drug released was determined by UV-Visible Spectrophotometer at 272 nm. The cumulative percentage drug release was calculated.

Figure 4: *In vitro* dissolution studies.

RESULTS AND DISCUSSION

Analysis of clopidogrel bisulfate by UV spectrophotometer:

The calibration curve of clopidogrel bisulfate was prepared in 0.1 N HCl and analysed at 272 nm using a UV-visible spectrophotometer. The absorbance increased proportionally with increasing drug concentration from 10 to 50 µg/mL, indicating a linear response. The absorbance values ranged from 0.12 at 10 µg/mL to 0.61 at 50 µg/mL. The calibration graph showed good linearity between concentration and absorbance throughout the selected range. This confirms that the developed UV spectrophotometric method follows the Beer–Lambert law within the studied concentration range. Therefore, the method is suitable for the quantitative estimation of clopidogrel bisulfate in 0.1 N HCl.

S.No	Concentration(µg/mL)	Absorbance
1	0	0.00
2	10	0.12±0.045
3	20	0.23±0.016
4	30	0.33±0.095
5	40	0.46±0.023
6	50	0.61±0.067

Table 3: Calibration curve of Clopidogrel bisulfate in 0.1N HCl (272 nm)

Calibration graph of Clopidogrel bisulfate in 0.1N HCl

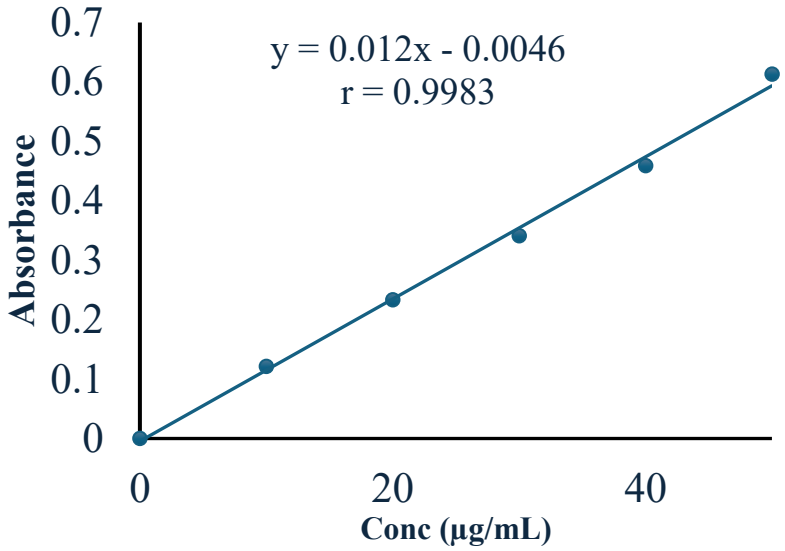

Figure 5: Calibration curve of Clopidogrel bisulfate in 0.1N HCl.

PRE-COMPRESSION PARAMETERS:

The pre-compression parameters of the bulk powder such as angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio were determined and the results were reported as shown in the table and these can be used for tablet manufacture. The pre-compression parameters of formulations F1–F6 were evaluated to determine their flow and compression characteristics. The angle of repose values (26–30°) indicated good flow properties for all powder blends. Bulk density, tapped density, Carr's index (10.26–12.70%), and Hausner's ratio (1.11–1.15) were within acceptable limits, suggesting good compressibility and flowability. Among all formulations, F6 showed the best flow properties with the lowest angle of repose, Carr's index, and Hausner's ratio. The results indicate that all powder blends possessed satisfactory micromeritic properties suitable for direct compression. Therefore, the prepared formulations were considered appropriate for further tablet compression and post-compression evaluation.

Formula-tion code	Angle of repose (θ)	Bulk density (gm/cm^2)	Tapped density (gm/ cm^2)	Carr's index (%)	Hausner's ratio
F1	28±0.45	0.68± 0.02	0.60± 0.02	11.76 ±0.35	1.13± 0.02
F2	29± 0.50	0.67± 0.03	0.59± 0.02	11.94 ±0.40	1.14± 0.02
F3	30 ±0.55	0.63± 0.02	0.55± 0.03	12.70± 0.45	1.15± 0.02
F4	29 ±0.48	0.65± 0.02	0.57± 0.02	12.31± 0.38	1.14± 0.02
F5	27± 0.42	0.75 ±0.03	0.67± 0.02	10.67 ±0.30	1.12± 0.01
F6	26± 0.40	0.78± 0.02	0.70 ±0.02	10.26± 0.28	1.11 ±0.01

Table 4: Pre compression parameters for the powder blend F1 and F6

POST COMPRESSION PARAMETERS:

The properties such as thickness, hardness, weight variation, *in-vitro* disintegration time, *in-vitro* dissolution studies were determined and the results were reported as shown in table 5. The prepared tablet formulations (F1–F6) were evaluated for postcompression parameters, including thickness, hardness, weight variation, friability, disintegration time and *in-vitro* drug release. The thickness of all formulations ranged from 3.0 ± 0.08 to 3.3 ± 0.10 mm, indicating uniform tablet dimensions. The hardness values varied between 5.0 ± 0.17 and 5.4 ± 0.15 kg/cm², confirming adequate mechanical strength. The average tablet weight ranged from 198 ± 0.70 to 201 ± 0.75 mg, and all formulations complied with pharmacopoeial limits for weight variation. Friability values were below 1% (0.45–0.70%), indicating good resistance

to abrasion during handling. The *in-vitro* disintegration time ranged from 1.5 to 3.5 minutes, with formulation F1 showing the fastest disintegration.

The dissolution studies demonstrated differences in drug release among the formulations. Formulation F1 exhibited the highest drug release, achieving 98.90% within 15 minutes, followed by F2 with 99.07% release in 25 minutes. Formulations F3, F4, F5, and F6 showed comparatively slower release, reaching 95.25%, 99.26%, 91.24%, and 86.23%, respectively, at 30 minutes. The rapid drug release observed with F1 may be attributed to its shorter disintegration time and lower friability, which enhanced water penetration and drug dissolution. Overall, all formulations met the required quality standards; however, F2 and F4 was identified as the optimized formulation due to its excellent post-compression characteristics, rapid disintegration profile and 90% was drug released in 30 mins. F2 containing 6% gum tragacanth and F4 containing 3% guar gum exhibited drug release within 30 minutes, indicating suitable release characteristics. F2 and F4 were compared with marketed formulation, which showed similar dissolution profiles. Natural gums like gum tragacanth and guar gum can be used for the preparation of clopidogrel bisulfate immediate release formulations at 6% and 3% concentrations respectively.

Formulation code	**Thickness (kg/cm^2)**	**Hardness (kg/cm^2)**	**Weight variation (mg)**	**%Friability**	***Invitro* disintegration time**
F1	3.0 ± 0.08	5.4 ± 0.15	199 ±0.65	0.45± 0.04	1.5± 0.20
F2	3.2± 0.07	5.0 ±0.18	201± 0.72	0.65 ±0.05	2.0± 0.12
F3	3.2± 0.09	5.1± 0.14	200 ±0.68	0.60 ±0.06	2.5± 0.10
F4	3.1± 0.06	5.2± 0.16	198± 0.70	0.55 ±0.05	2.5± 0.15
F5	3.3± 0.10	5.0 ±0.17	201± 0.75	0.70± 0.06	3.0± 0.18
F6	3.1± 0.07	5.3 ±0.13	199± 0.60	0.50± 0.04	3.5 ±0.20

Table 5: Post compression parameters from F1 to F6

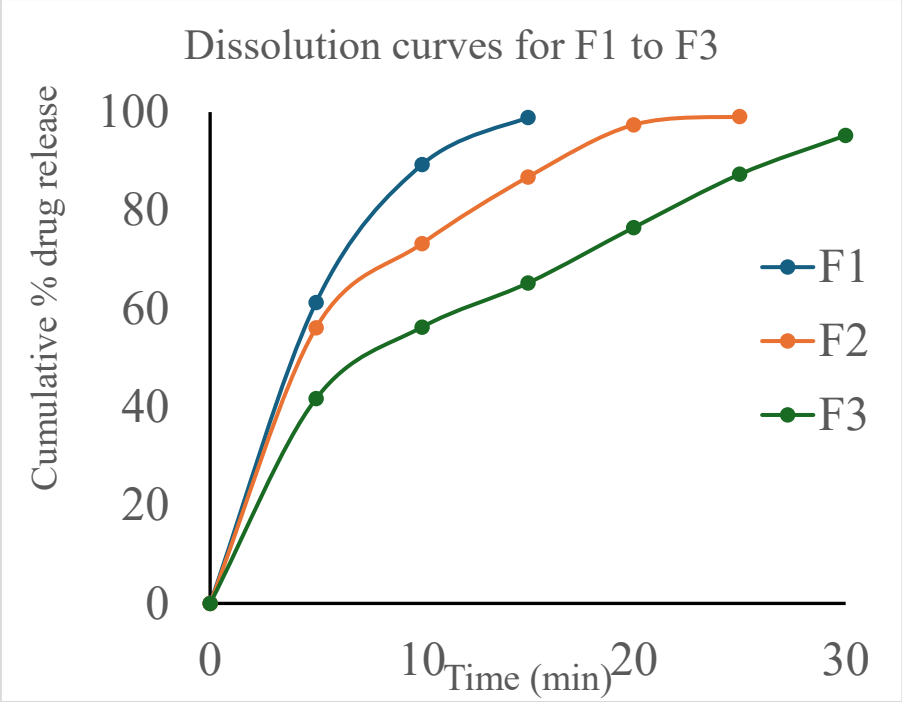

Figure 6: Dissolution curves for F1 to F3

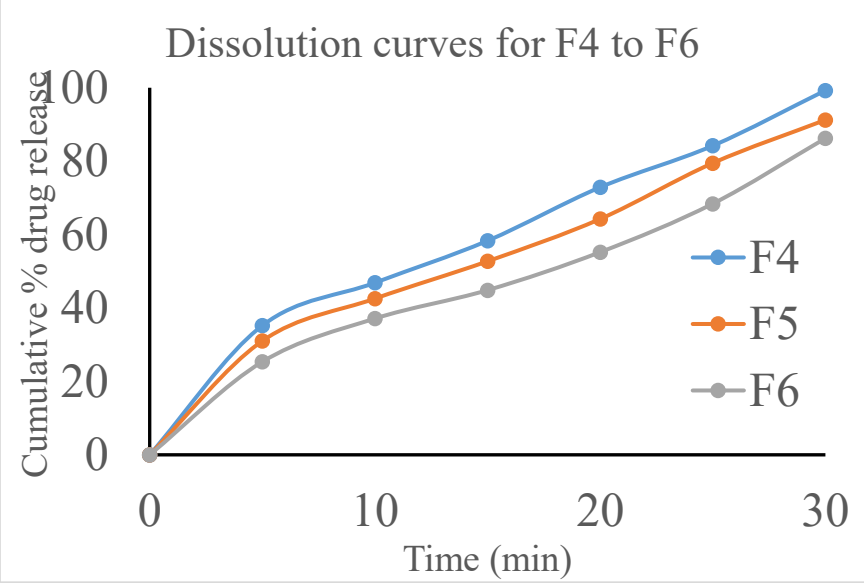

Figure 7: Dissolution curves for F4 to F6

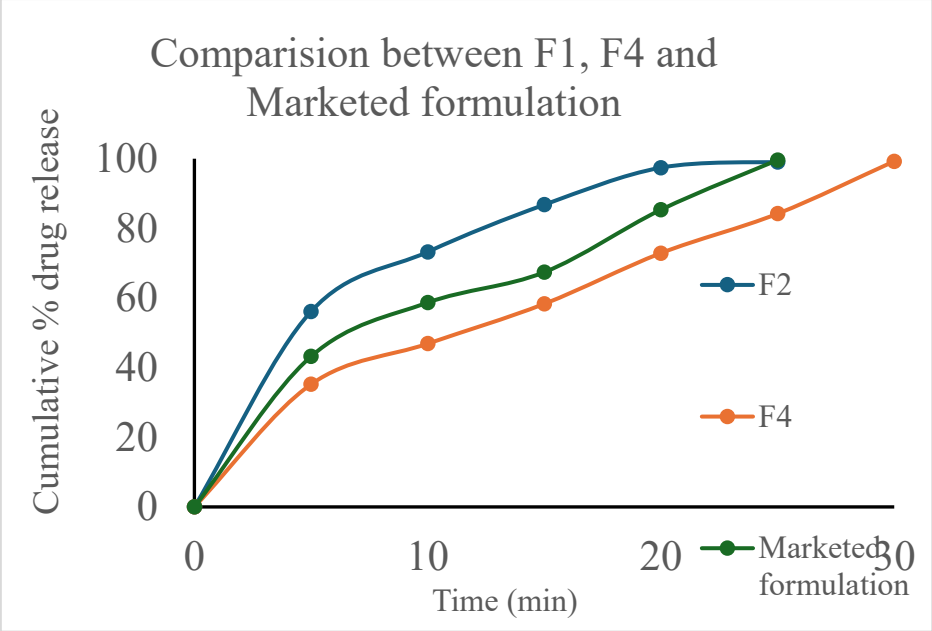

Figure 8: Comparison between F1, F4 and marketed formulation

CONCLUSION:

In the present research work, immediate release tablets of Clopidogrel bisulfate were successfully formulated using natural gums as excipients. The pre-compression blends of all formulations were evaluated for flow properties such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio, and the results indicated satisfactory flow characteristics. The compressed tablets were evaluated for physical parameters including weight variation, hardness, thickness, friability and all the formulations complied with pharmacopeial limits. *In-vitro* disintegration and dissolution studies revealed that formulations containing optimized concentrations of natural gums exhibited rapid disintegration and immediate drug release. Among all the formulations, the optimized formulation showed maximum drug release within a short period, confirming its suitability as an immediate release tablet. Hence, the developed immediate release tablets of Clopidogrel bisulfate using natural gums may improve bioavailability, patient compliance and therapeutic efficacy.

REFERENCE

1.Joshi R, Garud N, Akram W. Fast dissolving tablets: A review. Int J Pharm Sci Res. 2020;11(4):1562-70.

2.Shilpa S, Kumar A and Garigeyi PG: Formulation and optimization of Clopidogrel bisulfate immediate release tablet. International Journal of Pharmaceutical, Chemical and Biological Sciences 2012; 2(1): 38-51.

3.Shailesh S, Gurjeet S and Gupta AG: Formulation design and optimization of mouth dissolving tablets of Domperidone using the sublimation technique. International Journal of Pharmaceutical Sciences 2010; 1(1): 128-36.

4.Sharma D, Singh M, Kumar D and Singh AG: Formulation development and evaluation of fast disintegrating tablet of Cetirizine hydrochloride: A novel drug delivery for pediatrics and geriatrics. Journal of Pharmaceutics 2014; 1-8.

5.Patel U, Patel K, Shah D, Shah R. A review on immediate release drug delivery system. International journal of pharmaceutical research and bio-science. 2012; 1(5): 37-66.

6.Bhattacharjee A. Formulation and evaluation of immediate release tablets of bromocriptine mesylate by direct compression method. Indo american journal of pharmaceutical research. 2013; 3(3): 2841 – 2845.

7.Alton ME. Pharmaceutics the science of dosage form design. Second edition. churchill livngstone; 2002.

8.Gowtham M, Vasanti S, Rohan RD, Ashwath N, Paridhavi M. Formulation and evaluation of immediate release folic acid tablets. Scholars Research Library. 2011; 3 (6): 157-162.

9.Pathak N, Kumar A, Methkar V, Pant P, Rao RT. Formulation and optimization of immediate release tablet of an antialcoholic drug by dry granulation method. International Journal of comprehensive pharmacy. 2011;2(3) :1-4.

10.Sharma V, Arora V. Comparison of various superdisintegrants in the formulation of fast dissolving carvedilol tablet. International journal of pharmaceutical sciences and research. 2012 Oct 1;3(10):3947.

11.Bhusnure OG, Gholve SB, Giram PS, Thonte SS, Mane JM, Kazi PA, Bhange MA. Role of Superdisintegratings in fast dissolving tablets. International journal of pharmacy and pharmaceutical research. 2015;4(2):263-81.

12.Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009. (Clopidogrel drug profile, dosage form relevance)

13.Aulton ME, Taylor KMG. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 4th ed. Edinburgh: Churchill Livingstone Elsevier; 2013. (Immediate release tablet formulation & evaluation)

14.Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th ed. London: Pharmaceutical Press; 2009. (Natural gums as excipients, disintegrants, binders)

15.Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig JL, editors. The Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia: Lea & Febiger; 1986. p. 293–345. (Tablet formulation & evaluation tests)

16.Kumar R, Patil MB, Patil SR, Paschapur MS. Evaluation of disintegrating properties of natural gums in tablet formulation. International Journal of PharmTech Research. 2009;1(3):680–686.

17.Desai PM, Liew CV, Heng PW. Review of disintegrants and the disintegration phenomena. Journal of Pharmaceutical Sciences. 2016;105(9):2545–2555. (Immediate release & disintegration mechanism)

18.Nayak AK, Pal D. Natural polysaccharides in pharmaceutical formulations. Journal of Pharmaceutical Education and Research. 2010;1(1):1–14. (Natural gums in oral solid dosage forms)

19.Patil JS, Kamalapur MV, Marapur SC, Kadam DV. Formulation and evaluation of immediate release tablets using natural excipients. International Journal of Pharmaceutical Sciences and Research. 2011;2(6):1456–1461.

20.Shah VP, Tsong Y, Sathe P, Liu JP. In vitro dissolution profile comparison using similarity factor f2. Pharmaceutical Research. 1998;15(6):889–896.(Dissolution study justification)

21.Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Ghaziabad: IPC; latest edition. (Evaluation parameters, standards)

22.Goodman LS, Gilman A. The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011. (Clopidogrel pharmacology & therapeutic relevance)