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FORMULATION AND EVALUATION OF ORO DISPERSIBLE TABLET OF ESCITALOPRAM OXALTE BY SUPER DISINTEGRANTS ADDITION METHOD

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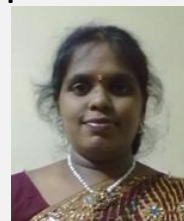
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ABSTRACT

The purpose of this research to develop oro dispersible tablet of escitalopram Oxalate. Oro dispersible tablet offers a solution for paediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance. Escitalopram oxalate has become a first line drug in the pharmacotherapy of patients with depression and several anxiety disorders. This because the drug is highly selective, more effective and better tolerated than other SSRIs. The aims is to formulate formulations of oro dispersible tablets by using various super disintegrants (Crospovidone, Kyron T-314, LHPC) in various combinations and fillers (Mannitol and Microcrystalline cellulose) by direct compression method. Less disintegration time and less in vitro dispersion time with formulation F7 it clearly shows that Crospovidone 5% and Kyron 7.5% as super disintegrants and Mannitol as diluent. From the above data's it has been found and concluded that crospovidone and Mannitol were suitable for the preparation of escitalopram oxalate oro dispersible tablets.

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Key Words

Escitalopram oxalate, Oro Dispersible tablet (ODTs), Super disintegrants and Direct compression.

INTRODUCTION

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance.

To overcome these drawbacks, mouth dissolving tablets (MDT) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/disperse in saliva within few seconds¹. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach used in development of MDT is the use of Superdisintegrants like Cross linked carboxy methylcellulose, Sodium starch glycolate, Polyvinyl pyrrolidone, crospovidone etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets.

The need for delivering drugs to patients efficiently and with few side effects has prompted pharmaceutical companies to engage in the development of new drug delivery system. A solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as fast dissolving dosage form or mouth dissolving tablets^[1]. ODT delayed release is a solid dosage form containing medicinal substances which disintegrates rapidly, usually within matter of seconds, when place upon the tongue, but which releases a drug (or drugs) at a time other than promptly after administration^[2, 3, 4]. When this type of tablet is placed into the mouth, the saliva will serve to rapidly dissolve the tablet. They are also known as oro-

dissolving, rapid –dissolve orodispersible, melt in mouth, rapimelt, quick dissolving, fast melts, and porous tablets.

For treatment of depression various conventional oral dosage forms like tablets, capsules, oral suspension, syrups etc are available in market but the major drawbacks with these are many patients find it difficult to swallow (dysphagia) tablets and hard gelatin capsules. The difficulty experienced in particular by paediatrics and geriatrics patients^[5]. Other groups that may experience problems include the mentally ill, developmentally disable and patients who are uncooperative and hence do not take their medicines as prescribed leading to patient noncompliance.

Escitalopram oxalate^[6] is selective serotonin reuptake inhibitor (SSRIs). SSRIs are broad spectrum antidepressants that are effective for major depressive disorder and several anxiety disorders. Escitalopram is highly selective, allosteric serotonin reuptake inhibitor. It has unique dual action mechanism involving allosteric and primary binding to serotonin transporter protein that explains the therapeutic superiority. Escitalopram Oxalate is highly selective, more effective and better tolerated than other SSRIs^[7]. The concept of formulating orally tablets containing escitalopram oxalate offers a suitable and practical approach in serving desired objective of rapid disintegration and dissolution characteristics with increased bioavailability. Hence the aim is to formulate orally disintegrating tablet of escitalopram oxalate, using various Superdisintegrants and fillers.

MATERIALS AND METHODS

Escitalopram oxalate (hetero drugs limited, Hyderabad), Crospovidone CL-F (shanhung industries Co.Ltd), LHPC-21 (SGN ETSU chemicals Co.Ltd), kyronT-314 (coral Pharma), Aspartame (neutrasweet company augusta), Orange, peppermint (Frimenich aromatics india PVT-LTD), lake sunset yellow (amerind colors& chemicals pvt.ltd), Aerosil 200 (wacker chemicals), Micro crystalline cellulose Ph-112 (FMC biopolymer), Mannitol SD200 (Merck Pvt.ltd), Talc (Nandhu chemical industries, huble).

FORMULATION OF ESCITALOPRAM OXALATE ODT

The oral disintegrating tablets of escitalopram oxalate were prepared using crospovidone, Kyrion T-314, L-HPC-21, used as super disintegrants microcrystalline cellulose and Mannitol used as diluents, aspartame as a

sweetening agent, powdarome orange and powdarome peppermint as flavour enhancer, aerosol and talc used as flow promoter. The composition of each batch shown in Table-1.

Table: 1 Formulation developmental trails

Ingredients / formulations	F1	F2	F3	F4	F5	F6	F7
Escitalopram Oxalate	20	20	20	20	20	20	20
Crospovione	5	5	10	10	10	10	10
LHPC-21	5	5	10	10	10	10	10
Kyrion-314	0	10	15	15	15	15	15
Aspartame	5	5	5	5	5	5	5
Powdarome Orange	5	8	8	8	8	8	8
Powdarome Peppermint	0	8	8	8	8	8	8
Lake Sunset Yellow	1	1	1	1	1	1	1
Aerosil	20	20	20	20	20	20	20
Micro Crystalline Cellulose	136	115	100	80	50	20	0
Mannitol	0	0	0	20	50	80	100
Talc	3	3	3	3	3	3	3
Total	200	200	200	200	200	200	200

Direct compression technique was selected for this formulation of ODT tablets, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration, in this process escitalopram oxalate, aspartame, orange, peppermint, LHPC-21 were together passed through sieve no 40 (Blend-1). MCC& aerosil were together passed through sieve no 40 (Blend-2). lake sunset yellow was passed through the sieve no 80. The three blends are mixed and co shifted through sieve no 40. blend for 5 mins magnesium stearate was added and blended for 10 mins. The final blend was compressed into tablets by using 8mm flat bowled edge punches with break line.

EVALUATION PARAMETERS OF ESCITALOPRAM OXALATE ODT:

Estimation of escitalopram oxalate:

An UV Spectrophotometric method based on the measurement of absorbance at 239nm in methanol was used in the estimation of escitalopram oxalate. The method obeyed Beer's law in the

concentration range of 2-10µg/ml. Low RSD values ensured reproducibility of the method. Thus the method was found to be suitable for the estimation of escitalopram oxalate content in various products and in vitro dissolution studies.

Evaluation of pre compression parameters of the powder:

Prior to compression, granules were evaluated for their flow and compressibility parameters. Flow properties of granules were determined by angle of repose method. Compressibility index of granules were determined by Carr's index and Hauser ratio^[8-9].

Evaluation of post compressional parameters of the tablets^[10]

Physical appearance

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour etc.

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The tablet thickness should be controlled within a $\pm 5\%$ variation of a standard.

Weight variation

20 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 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Average weight of tablet (mg)	% difference
130 or less	10 %
From 130 to 324	7.5%
> 324	5%

Hardness test

The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm².

Percentage friability

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping. **Method:** If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets were tested.

$$\% \text{Friability} = \frac{(\text{Initial weight of tab} - \text{Final weight of tab})}{\text{Final weight of tab}} \times 100$$

Disintegration time

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus

containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at $37 \pm 2^\circ\text{C}$. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30seconds.

Wetting time and water absorption ratio:

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure⁵⁵. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio, *R* can be the determined according to the following equation. $R = 100 (W_a - W_b) / W_b$

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH6.8). Six tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Dissolution studies

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

Method: The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15 and 30 min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

RESULTS AND DISCUSSION

The escitalopram oxalate API was scanned in the UV between 200-400 nm observed that at 239nm shows maximum absorbance. Shown in figure-1 the standard calibration curve was plotted the concentration 2-10µgm/ml the slope observed 0.38 intercept 0.003 and correlation (R) was 0.999 respectively shown in figure-2. The pre compressional parameters show that the pure drug posses the poor flow property was shown in Table-2. The flow properties of the blend were show in the Table-3.

Table 2: Flow properties of API

S.NO	TEST	RESULT
1	Bulk density(g/ml)	0.200gm/ml
2	Tap density(g/ml)	0.384
3	Compressibility Index	48%
4	Hausner Ratio	0.1923
5	Angle of Repose	44.645

Table 3: Pre-compressional parameters

BATCH NOS	F1	F2	F3	F4	F6	F7	F8
Angle of repose	48.32	37.45	34.76	32.98	32.56	29.65	28.98
Bulk density	0.25	0.605	0.631	0.586	0.384	0.486	0.463
Tap density	0.384	0.741	0.728	0.681	0.45	0.532	0.509
Compressibility index	34.89	18.35	13.32	13.95	14.66	8.64	9.03
Hausner ration	1.53	1.22	1.15	1.16	1.17	1.09	1.09

Figure1: UV graph of escitalopram oxalate

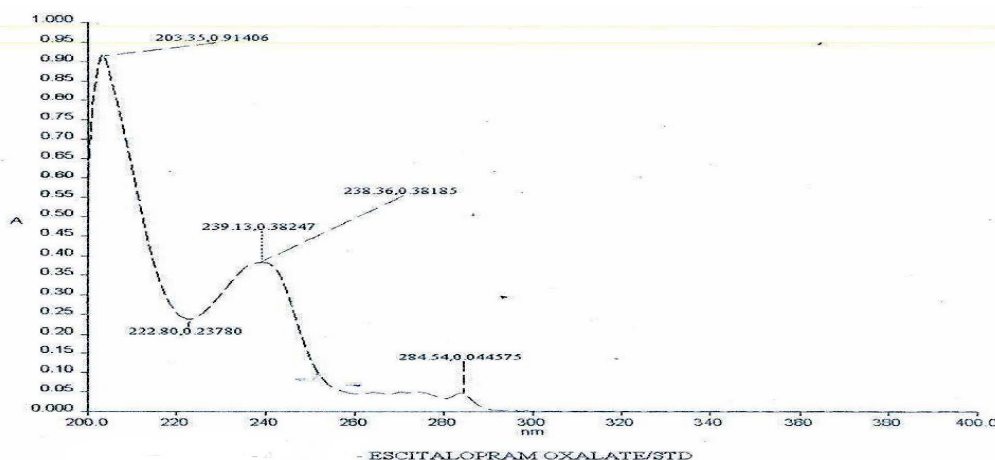
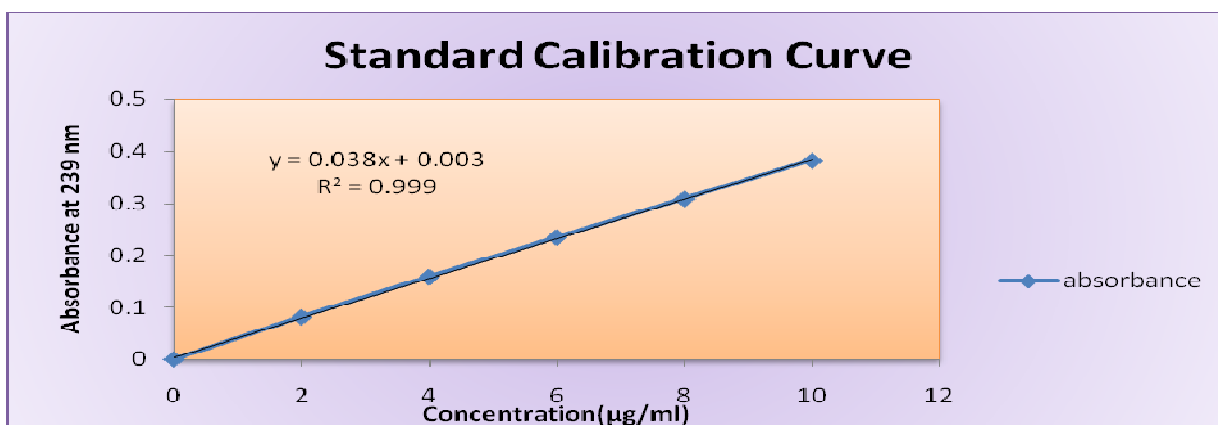


Figure 2: standard calibration curve of escitalopram oxalate



The formulations F1 was prepared using Crospovidone (2.5%) and LHPC (2.5%) as super disintegrants and MCC as diluent shows disintegration time more than 3mins and invitro dispersion time more than 7min. the increased concentrations of super disintegrants up to 7.5% and addition of Kyron T-314 in the next trails F2, F3 results in decreased in disintegration time but no improvement in the in-vitro dispersion & wetting times which was most important in the oro dispersible tablet. The addition of Mannitol and increased concentration of aerosil 10% in the F4 results more improvement in the disintegration, dispersion &

wetting time. Further increasing concentration of Mannitol F5 results in good dispersion and wetting time. Finally the micro crystalline cellulose was replaced by Mannitol in F7 as a diluent results good in dispersion, wetting and disintegration times. post compressional parameters shown in Table-4. F7 was carried out by using Crospovidone, KyronT-314, LHPC-21 were used as the Superdisintegrants and Mannitol as filler results disintegration time 15±3 secs in vitro dispersion time 31 seconds and wetting time 28 seconds. Hardness of the tablet between 3-4, and friability of 0.09% was observed.

Table4: Post- Compressional Parameters

Formulati on Code	Average weight (mg) ±7.5%	Thickness (mm) ±5%	Hardness (kp)	Percentage Friability (%) 0.1-0.9%	In vitro Disintegrati on Time (sec)	In vitro dispersion time(sec)	Wetting time (sec)
F1	201	3.55	2.5	0.31	180	>7min	240
F2	199.6	3.54	2.3	0.20	68	132	118
F3	202.5	3.71	2.0	0.22	55	121	110
F4	200	3.89	2.2	0.10	49	65	45
F5	201	3.67	2.5	0.11	21	45	48
F6	199	3.71	3.4	0.09	18	34	24
F7	200	3.70	3.5	0.09	16	31	28

In vitro release studies was carried out using USP apparatus Type II (paddle) method at $37 \pm 2^\circ\text{C}$ taking 900 ml of 0.1N HCl as dissolution medium, the speed of the paddle was set at 50 Rpm. The samples were withdrawn

at 5, 10, 15 and 30mins time interval. The samples were analyzed for the percentage drug release. Comparative Invitro dissolution profiles shown in Figure-3 and Figure-4.

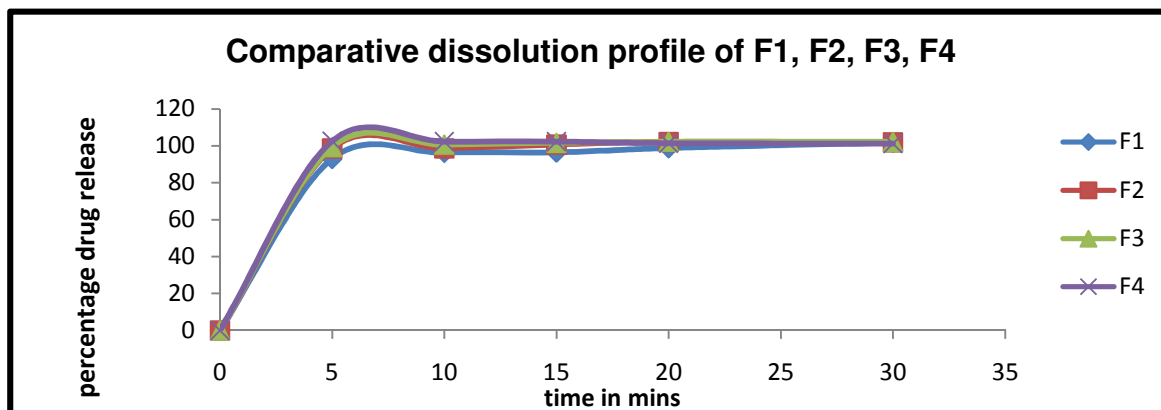
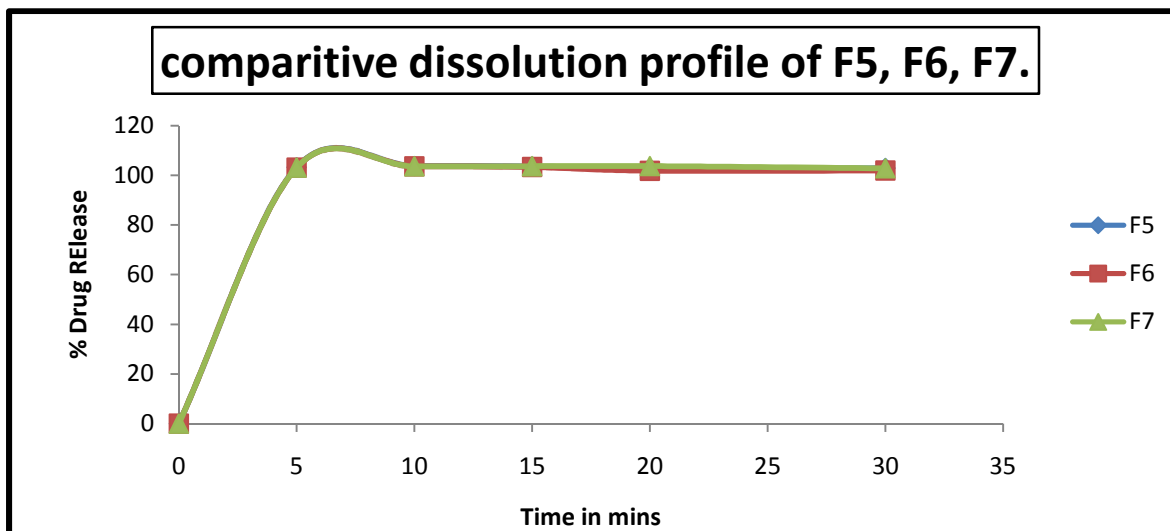


Figure 4:



Formulations were prepared by direct compression technique the final tablets of the initial trails shows 90% drug release at the end of the 5 min and 100% at the end of the 20 mins the final trails F5, F6, F7 shows the 100%drug release at the end of the 5 min. The rapid drug dissolution might be due to easy breakdown of particles due to porous structure formation by direct compression of blend and rapid absorption of drugs into the dissolution medium.

CONCLUSION

Oral disintegrating tablets (ODT) of Escitalopram oxalate is successfully prepared by using direct compression method, undoubtedly the availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance, low dosing and rapid onset of action, fast disintegration, low side effect, good stability and its popularity in the near future. For treatment of depression various conventional oral dosage forms like tablets, capsules, oral suspension, syrups etc are available in market but

the major drawbacks with these are many patients find it difficult to swallow (dysphagia) tablets and hard gelatin capsules. ODT is most suitable dosage form because of its use without need of water. From the study, it can be concluded that direct compression method showed better disintegration. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the patient compliance at emergency and the absorption leading to its increased bioavailability. Direct compression technique would be an effective and simple alternative approach in industrial scale compared with the use of more expensive process and adjuvant in the formulation of oral disintegrating tablets.

From the study we can conclude that Crospovidone 5% and KyronT-314 7.5% used as super disintegrants and Mannitol as diluent shows good wetting time (24 sec) fastest disintegration (14 sec) and 100% drug release within 5 mins so these super disintegrants and diluent suit for the preparation of escitalopram oxalate oral disintegrating tablet.

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REFERENCES

1. D. Panagrahi*, S. Baghel, S.B. Mishra, "Mouth dissolving tablets – An overview of preparation techniques, evaluation and patented technologies", *Journal of pharmacy Research*, Vol 4, 33-38, 2005.
2. Guidance for industry oral disintegrating tablets published by centre for drug evaluation and research, accessed at <http://www.fda.gov/cder/guidance/index.htm>
3. <http://www.FDA.gov>- CDER Data standards manual.
4. European Pharmacopeia; 2006, p.3151-56.
5. S. Gilbert*, S. Banker, C. T. Rhodes, *Modern pharmaceuticals*, Marcel Dekker Inc, New York 1996, pp. 372-379.
6. Rx list the internet drug index lexapro escitalopram oxalate drug description and clinical pharmacology.
7. Drugs.com The drug information online escitalopram oxalate.
8. Carter SJ. Eds: In Copper and Gun's: Tutorial Pharmacy, 6th ed., CBS Publishers and Distributors, Delhi, 1998, pp. 225.
9. Aulton ME. Eds: *Pharmaceutics: The science of dosage form design*, 1st ed., Churchill Livingstone, London, 1998, pp.247,
10. Lachman L, Lieber HA. *Pharmaceutical dosage forms of tablets*. Vol II, Marcel Dekker, 1981, pp.241-243.
