Formulation & Evaluation of Tablet Based on Solid Dispersion of Antihistaminic Drug

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Abstract- In this Study Orodispersible tablets of Cimetidine was prepared by compressing granules that were successfully prepared by wet granulation method with sodium starch glycolate and crosspovidone as superdisintegrant and other excipents like camphor, mannitol, polyvinylpyrrolidine, Talc and Mg stearate. Preformulation studies of the drug were performed first and the results were found to be the drug is white in colour and odourless. The solubility of the drug was found to be it is soluble in water and 0.1 N HCl, sparingly soluble in dimethyl sulfoxide and insoluble in chloroform and methanol. The melting point and partition coefficient were determined by open capillary method and phase separation method. The melting point and partition coefficient of the drug were found to be 140˚C and 2.4.The UV absorbance's of Cimetidine standard solution in the range of 5-50 µg/ml of drug in water showed linearity at λ max 218nm. The linearity was plotted for absorbance against concentration with R2 value 0.973 and with the slope equation y = 0.032x + 0.011.A granule prepared by wet granulation was subjected to the evaluation of their flow property like angle of repose, bulk density, tapped density, carr's index and hausner's ratio. The results were found to be in the limits. After mixing the powder with appropriate characteristics and flow property, tablets were made by direct compression method in a single punch machine. All the prepared tablets were evaluated for the test like hardness, friability, weight variation, disintegration time, drug content and dissolution studies. Hardness friability was found to be in limits. According to the European Pharmacopoeia standard for orodispersible tablets,

Keyword- Tablet, Orodispersible Tablet, Antihistaminic Activity

INTRODUCTION

The oral route of administration still remains as the most favoured route despite tremendous innovations in drug delivery such as parenteral, transdermal, nasal, etc., (Gauri *et al.,* 2012). This is due to its various advantages such as the ease of ingestion, less pain, accurate dosage, self-medication potential, versatility, most essentially and patient compliance (Rajeev *et al.,* 2013). It is the most frequent used route of drug delivery as well as it being generally considered to be the most convenient and economic because it carries the lowest cost (Bardelmeijer *et al.,* 2000). These characteristics have given the oral route to be a wide acceptance among patients and represents up to 50-60% of the total possible dosage forms. However, some drugs can cause gastrointestinal tract irritation. Difficulty in swallowing conventional tablets is one of the essential problems of this dosage form. Additionally, pediatric and geriatric patients also experience difficulty and inconvenience of swallowing. Since drinking water plays an important role in the swallowing of oral dosage forms, patients might experience an inconvenience to swallow the tablet when water is not available, such as in the case of motion sickness (kinetosis), sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention (Prabhakar *et al.,* 2012).

Orodispersible Tablet

Orodispersible tablets (ODTs) can be defined as solid single unit dosage forms that are intended to be placed in the mouth and then swallowed without the need of water. The tablet will disperse or dissolve in the saliva instantaneously, within seconds and swallowed easily as residue with no difficulty. The faster the drugs disintegrate and dissolution occurs, the quicker the absorption and onset of clinical effect. Lozenges, buccal, and chewable tablet are also some of solid oral dosage form that can be used without water intake. However, there are differences in the drug release methodology between them. In comparison to ODTs, Lozenges and buccal tablets are intended to dissolve

slowly in the mouth, whereas, chewable tablets have a longer disintegration time and require chewing action by the patients before they can be swallowed. ODTs have become a favoured alternative to conventional oral dosage forms such as tablets and capsules and other liquid pharmaceutical preparations over the past three decades. Orodispersible tablets, rapidly disintegrating tablets, fast dissolving tablets, mouth dissolving tablets, melt in the-mouth, fast dissolving drug delivery, quick dissolving tablets are some of the names that have been used as synonyms for orodispersible tablets. The European pharmacopoeia approved term was "orodispersible tablets" They defined it as a tablet that is placed in mouth where it disperses rapidly before swallowing (Sreenivas et al., 2005). According to USFDA, the ODT tablets where defined as solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue. It has been proven statistically that ODTs have several advantages over conventional tablets to enhance patient compliance and acceptance because of its feasibility and convenience. Almost 50% of the population suffers from difficulty swallowing while taking tablets and hard gelatin capsules. These populations include pediatric and geriatric populations who have difficulty swallowing large tablets. In order to overcome these problems, mouth dissolving tablets (MDT) or orodispersible tablets (ODT) have been developed as alternative oral dosage forms (Dixit et al., 2012). Accordingly, ODTs became an excellent choice as a new drug delivery system, because they are easy to administer and lead to better patient compliance, especially in the elderly and children. Orodispersible tablets have become very attractive for even active people who do not suffer from any swallowing problems. Specialized peel off blister packaging is required for fast dissolving tablets since they are very fragile and friable. ODT technologies have been developing very rapidly over this past decade. There are new generations of ODT which have been advanced to overcome the limitations of the earlier products. Some companies provided technologically advances to produce pleasant tasting tablets to overcome the common problem of poor drug taste which compromised the benefits of the ODTs. Other companies developed new technologies to improve the controlled release of ODTs. The ease of manufacture and fewer risks associated with fast dissolving tablets have made ODT technology an excellent choice for most pharmaceutical manufacturing. Another factor which makes ODTs highly favorable is the route of administration that it has only administered by mouth. This one factor allows other companies to get approval for a generic version of the drug (Ghosh *et al.*, 2011).

Criteria for orodispersible tablets (Modi *et al.*, 2006)

- ODTs disintegrate/dissolved within few seconds once placed in the mouth, which as a result can be taken with or without the requirement of water
- They are compatible with taste masking and other excipients.
- ODTs have pleasant mouth feel and leave minimal or no residue in the mouth. This can be very helpful in order to avoid the bitter taste of the drugs, particularly for pediatric patients.
- ODTs provide good stability since they exhibit less sensitivity to environmental conditions.

Technologies used for manufacturing ODTs

In the recent past, several new advanced technologies have been introduced for the manufacturing of ODT. Some of these technologies are patented and some are not.

Freeze drying or lyophilisation

This is a process of preparing an orally disintegrating tablet containing pharmaceutically active substance by removing solvent from a solution or suspension of drug. Suspension can be a continuous phase of coarse particles of pharmaceutically active substance in a carrier material, reducing the temperature of the suspension to increase the viscosity of suspension and minimize sedimentation of particles. This forms discrete units of the cooled suspension. Continuous phase can be removed to produce rapidly disintegrating forms (Badgujar *et al.*, 2011).

Molding

Molded tablets have quick dissolution, accepted stability and taste. This dosage form is suitable for the administration of drugs with unpleasant taste. The tablet triturate form includes a cementary network constituted by a water soluble but ethanol insoluble carbohydrate (Badgujar *et al.*, 2011).

Cotton candy process

This involves the formation of a particulate support matrix which dissolves or disintegrates in few seconds, when placed in aqueous environment. First step consists of formation of a porous particulate powder matrix. In the second step, drug and additives are added to the mixture. Third step consists of converting this mixture into tablet (Badgujar *et al.,* 2011).

Spray drying

Process involve the formulation of a particulate support matrix for making tablet which dissolve or disintegrate in a matter of few seconds once placed in the oral cavity. The support matrix can be comprised of two polymeric components, one may be non hydrolysed gelatin and the second may be a hydrolysed gelatin and a bulking agent. The porous particulate powder can serve as the tablet support matrix, to which the drug can be added (Badgujar *et al.,* 2011).

Melt granulation

In this method a hydrophilic waxy binder, superpolystate is made use of . This material not only acts as a binder but also helps in the disintegration 5 of tablets as it melts in mouth and solubilises very rapidly without leaving residues (Abdelbary *et al.,* 2004).

Direct compression method

This is the most popular method for the manufacture of ODTs. This may be due to the reasons like, it is the simplest and cost-effective tablet manufacturing technique. We require only the conventional tablet manufacturing and packaging machine. Excipients with improved flow, compressibility and disintegration properties such as disintegrants are easily available (Arya *et al.,* 2010).

METHODS OF PREPARATION

Fusion method

The melting or fusion method was first proposed by Sekiguchi and Obi. The physical mixture of the drug and water soluble carrier was heated until it melted. The melted mass then immediately cooled and solidified in an ice bath under rigorous stirring. The resultant mass was crushed pulverized and sieved. This method is a simpler and cheaper method. But the technique is applicable only if the drug and carrier are compatible with each other, mix homogeneously when heated and solidified and should not get degraded at higher temperature used for melting (Tran *et al.,* 2019).

Solvent evaporation method

In this method, the drug and the carrier are dissolved in a common solvent. The solvent is evaporated to obtain the solid dispersion. The main advantage of this technique is that, there is no chance of thermal decomposition of the drug, since minimal or no heat is applied for the evaporation of the solvent. The major limitations of the technique are high cost and the incomplete removal of solvent which may affect the drug adversely (Tran *et al.,* 2019).

Melt extrusion method

This technology makes use of high shear and high temperature for the formulation of solid dispersion. A twin shell extruder is typically used. Advantages are solvent free continuous process and relatively feasible scale up (Tran *et al.,* 2019).

Supercritical fluid process

A supercritical fluid (SCF) can be defined as a substance existing as a single fluid phase above its critical temperature and pressure. Among the supercritical fluids, CO2 has been widely used. This is because of its nontoxic, nonflammable and inexpensive nature. It has high dissolving power and low critical parameters. This method includes dissolving the drug and carrier in a solvent common to both and introducing into a particle formation vessel through a nozzle, along with CO2. The solution when sprayed the solvent is extracted by the SCF, which leads to the precipitation of solid dispersion particles (Tran *et al.,* 2019).

Preparation of Standard Curve of cimetidine in water

Accurately weighed 50 mg of cimetidine and it was taken in 50 ml volumetric flask and dissolved in 2-3ml water and volume was made up with water to the mark .The resulted 1000µg/ml stock solution .From the above stock solution 10ml was taken in another 100ml volumetric and volume was made up with water to mark and the concentration of solution become 100µg/ml. After that from the above solution the aliquots of 1-10ml of stock solution were taken into a series of 10ml volumetric flask and volume was made

up to the mark with water and it was analysed at λmax 218 nm using UV spectrophotometer. The standard curve was plotted between absorbance and concentration.

Development of cimetidine granules

The orodispersible tablets of cimetidine were prepared using superdisintegrant (SSG, and crospovidone), subliming agent (camphor), mannitol as a diluent, sodium saccharin as sweetening agent, alcoholic solution of polyvinylpyrrolidone (PVP) in ethanol (10%, *w*/*v*) as binder and talc with magnesium stearate, as a flow promoter. The drug and other ingredients were mixed together, and a specified volume of alcoholic solution of PVP (10%, *w*/*v*) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 10 and dried in a tray dryer at 65°C for 10 min then screened through sieve no. 18. The dried granules were then blended in a tumbling cylindrical blender with talc, and magnesium stearate (Abed *et al.*, 2010).

Table 1 Composition of granules

S. No.	Ingredients(mg)	Formulations				
		F1	F2	F3	F4	F5
1	Cimetidine	80	80	80	80	80
2	Sodium starch glycolate	100	150	-	-	-
3	Crosspovidone			100	150	-
4	Camphor	10	10	10	10	10
5	Sodium saccharine	2	2	2	2	2
6	Magnesium stearate	10	10	10	10	10
7	Talc	20	20	20	20	20
8	mannitol	100	100	100	100	100

RESULT AND DISCUSSION

Pre formulation studies

Pre formulation studies were performed. The result is given below.

Organoleptic evaluation

In organoleptic evaluation of drug, colour, odour, and appearance were evaluated.

Table 2 Organoleptic evaluation of cematidine

Drug	Organoleptic properties	Observation
Cematidine	Color	White to pale yellow
	Odor	Odorless
	Appearance	Crystalline powder

Discussion

The above table is depicted that the drug cematidine is white to pale yellow in colour, odourless and crystalline powder.

Solubility study

Results of the solubility studies are given below.

Table 1 Solubility of cimetidine

Drug	Solvents	Observation/Inference
Cematidine	Dimethyl sulfoxide	Sparingly soluble
	Water	Soluble
	Chloroform	Insoluble
	Methanol	Insoluble
	0.1 N HCl	Soluble

Discussion

The drug is found to be soluble in water and 0.1 N HCl, sparingly soluble in dimethyl sulfoxide and insoluble in chloroform and methanol.

Melting point determination

Table 3 Melting point of cimetidine

S. No.	Drug	Observed	Reference
1	Cimetidine	140°C	140-143° C

Discussion

Melting point of cimetidie was found to be 140˚C.

Partition Coefficient

Table 4 Partition Coefficient of cimetidine

S. No.	Medium	Log P
1	n-octanol:Water	2.4

Discussion

Partition coefficient of the drug was found to be 2.4 in n-octanol: water.

Determination of λ max

Solution was scanned under UV-Vis Spectrophotometer and λ max was determined. It was found to be as per the monograph.

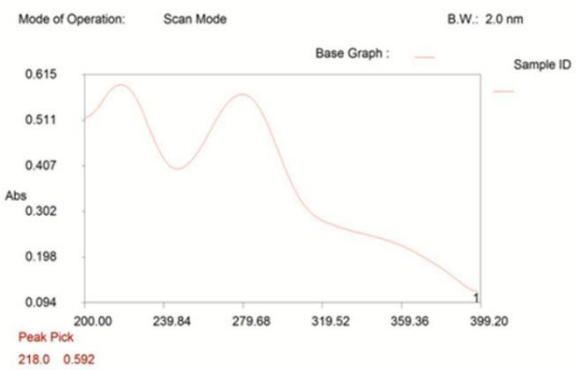

Figure 1 λmax of cimetidine

Standard calibration curve of Cimetidine

Table 5 Calibration curve of Cimetidine

Concentration (µg/ml)	Absorbance (218 nm)
5	0.155
10	0.386
15	0.432
20	0.695
25	0.758
30	0.998

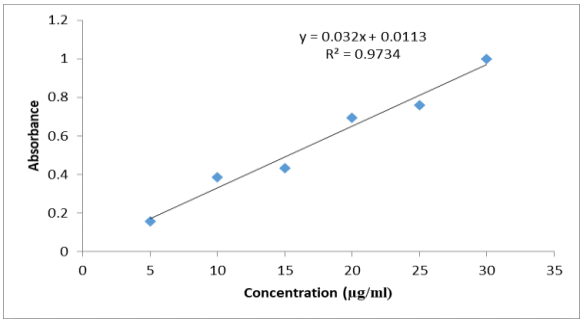

Figure 2 Calibration curve of cimetidine

Discussion

Seven points calibration curve were obtained in a concentration range from 5-30 µg/ml for drug. The response of the drug was found to be linear in the investigation concentration range and the linear regression equation was y = 0.032x + 0.011 with correlation coefficient $R^2 = 0.973$.

Powder Property

Flow property of the granules was performed by different parameters like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio and the results are given below.

Table 6 Results of flow property of granules

Flowability property	Formulations				
	F1	F2	F3	F4	F5
Angle of repose	30.46	31.64	32.75	31.46	33.57
Bulk Density	0.784	0.648	0.847	0.964	0.738
Tapped density	0.274	0.253	0.358	0.412	0.263
Compressibility index	20.57	21.48	22.48	20.25	21.58
Hausner´s ratio	1.20	1.25	1.11	1.23	1.27

- Angle of Repose

Angle of repose of extract blend was found in the range of 30º to 33°. These values are well within the limit of 25º – 30° which indicates the flow of extract granules was good. The above results revealed that the all the formulations (F-I to F-5) possess good flow.

- Bulk Density and Tapped Density

Bulk density of extract was found between 0.64 to 0.96 g/cm3. Tapped density ranges between 0.25 to 0.41 g/cm3.

Compressibility Index and Hausner's Ratio

Compressibility index values was found to be in the range of 20.25 to 22.48 % and the hausner,s ratio lies between 1.11 to 1.27.

- Cimetidine orodispersible tablet assessment

Evaluation of the different batches of the tablets was performed for hardness, friability test, and weight variation. Disintegration time and % drug content. The results are given below.

Table 7 Results of post compression evolution

Evaluation parameters	Formulations				
	F1	F2	F3	F4	F5
Hardness (Kg/cm^2)	3.5	3.0	3.7	3.2	3.3
Friability %	0.467	0.538	0.496	0.648	0.368
Weight variation (gm)	3.26	3.84	2.95	2.25	3.16
Disintegration time (seconds)	22	25	27	18	26

Discussion:

- Hardness (kg/cm^2)

The hardness test was carried out by using monseto tester. The hardness values of formulations (F-1 to F-5) were found to be in the range of 3.0 to 3.7 respectively. Hence all the tablets passed the hardness test.

- Weight Variation Test

Five tablets of each formulation were randomly selected for weight variation test. The accepted percentage deviation was ± 7.5 for 130 – 324 mg tablet weight as per I.P. The results showed that the weight of tablets ranges from 2.25 to 3.84 for all the formulations that is well within the I.P limit (± 7.5). Hence all the tablets passed the weight variation test.

- Friability Test

The friability test carried was out by using Roche friabilator. The maximum weight loss should not be more than 1%. The friability values of formulations (F-I to F-5) were found to be in the range of 0.368 to 0.648 respectively. Hence all the tablets passed the friability test.

In-vitro drug release

Table 8 *In vitro* evaluation percentage of drug release

Time in minutes	Formulations (%)				
	F1	F2	F3	F4	F5
2	15	16	13	15	12
4	25	24	22	23	20
6	37	30	30	33	39
8	43	41	38	42	47
10	58	55	45	54	52
15	63	62	56	61	60
20	72	75	63	70	68
30	80	83	71	79	75
45	89	90	80	87	82
60	98	97	95	94	90

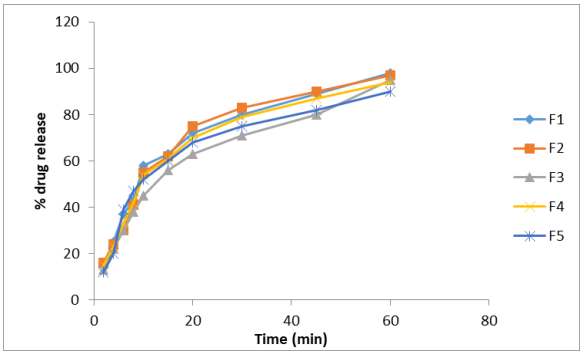

Figure 3 Cumulative % drug release

Discussion

In vitro drug release profiles for all formulations were carried out by using 7.4 pH phosphate buffer as dissolution medium for about 60 minutes. From the above results it was found that the release of drug from formulation F1 gave the better release.

Kinetic studies

Since formulation F1 showed highest drug release so it was selected for the kinetic studies.

Table 9 Release kinetics study of F1 formulation

Formulation	Model	Kinetic parameter values
F1	Zero Order	y = 1.289x + 32.20 R^2 = 0.815
	First Order	y = -0.025x + 1.969 R^2 = 0.964
	Higuchi	y = 13.27x + 4.312 R^2 = 0.950

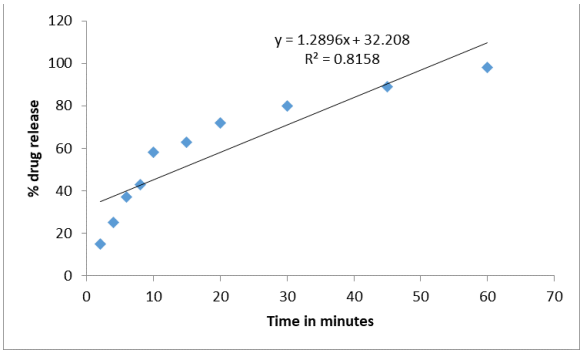

Figure 4 Zero order model of F1 formulation

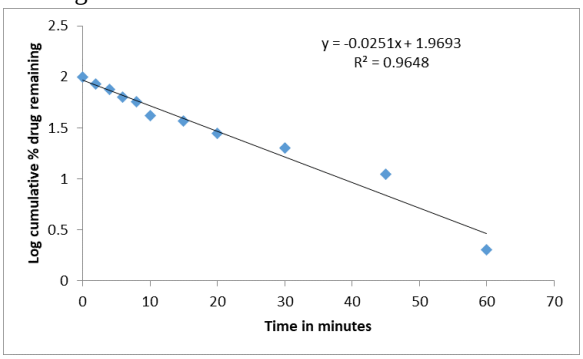

Figure 5 First order model of F1 formulation

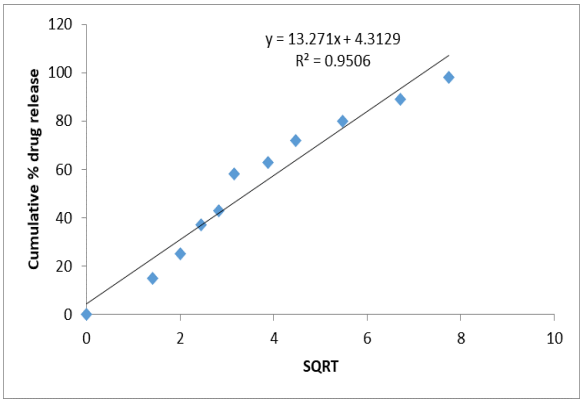

Figure 6 Higuchi model of F1 formulation

Discussion

Zero order kinetic model refers to the process of constant drug release from a drug delivery device independent of the concentration. The zero order graph of F1 formulation showed the constant drug release from the tablets, the results of the zero order model was found to be y = 1.289x + 32.20, R2 = 0.815. The first order kinetic model describes the release from system where release rate is concentration dependent. The results of first order kinetic model was found to be y = -0.025x + 1.969, R2 = 964. The Higuchi model is used to describe the limits for transport and drug release. The Higuchi model of tablets was found to be y = 13.27x + 4.312, R2 = 0.950.

SUMMARY

Orodispersible tablets of Cimetidine was prepared by compressing granules that were successfully prepared by wet granulation method with sodium starch glycolate and crosspovidone as super disintegrant and other excipients like camphor, mannitol, polyvinylpyrrolidine, Talc and Mg stearate. Preformulation studies of the drug were performed first and the results were found to be the drug is white in colour and odourless. The solubility of the drug was found to be it is soluble in water and 0.1 N HCl, sparingly soluble in dimethyl sulfoxide and insoluble in chloroform and methanol. The melting point and partition coefficient were determined by open capillary method and phase separation method. The melting point and partition coefficient of the drug were found to be 140˚C and 2.4.The UV absorbance's of Cimetidine standard solution in the range of 5-50 µg/ml of drug in water showed linearity at λ max 218nm. The linearity was plotted for absorbance against concentration with R2 value 0.973 and with the slope equation y = 0.032x + 0.011.A granule prepared by wet granulation was subjected to the evaluation of their flow property like angle of repose, bulk density, tapped density, carr's index and hausner's ratio. The results were found to be in the limits. After mixing the powder with appropriate characteristics and flow property, tablets were made by direct compression method in a single punch machine. All the prepared tablets were evaluated for the test like hardness, friability, weight variation, disintegration time, drug content and dissolution studies. Hardness friability was found to be in limits. According to the European Pharmacopoeia standard for orodispersible tablets, the disintegration time should not be more than 10 min. All the formulations were disintegrated within these limits but the formulation F1 disintegrated in 22 sec; it concluded that the F1 formulation was found to be the best one.In-vitro drug release studies were evaluated for drug release by using USP dissolution test apparatus, F1 formulation showed 98% drug release among all the formulations within 60 minutes. It concluded that F1 formulation showed good in-vitro dissolution as well as disintegration. This study confirms that cimetidine can be successfully prepared in the form of sustained release tablets by compressing granules that were prepared by wet granulation method with excipients.

CONCLUSSION

Orodispersible tablets of Cimetidine formulation system include the drug delivery system that achieves fast and immediate release of the drug over the short period of time. orodispersible tablets of cimetidine have been successfully formulated using sodium starch glycolate and crosspovidone as disintegrating agent. Overall, the results suggested that suitably formulated orodispersible tablets of cimetidine containing sodium starch glycolate as a super disintegrant and camphor as a subliming agent by wet granulation method can be achieved. The wet granulation method shows superior flow properties over direct compression method. The optimum selected formula (F1) has satisfactory fast *in vitro* disintegration time, high dissolution rate, and appreciable buccal absorption and good stability.

REFERENCES

[1] Abdelbary G, Prinderre P, Eouani C, Joachim J, Reynier JP, Piccerelle P. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. International Journal of Pharmaceutics. 2004; 278(2): 423-33.

[2] Abed, K. K., Hussein, A. A., Ghareeb, M. M., & Abdulrasool, A. A. (2010). Formulation and optimization of orodispersible tablets of diazepam. *AAPS PharmSciTech*, *11*(1), 356–361. https://doi.org/10.1208/s12249-010-9387-y

[3] Arya Arun, Chandra Amrish. Fast drug delivery systems: a review. Der Pharmacia Lettre. 2010; 2(2): 350-361.

[4] Badgujar BP, Mundada AS. The technologies used for developing orally disintegrating tablets: a review. *Acta Pharm*. 2011;61(2):117-139. doi:10.2478/v10007-011-0020-8

[5] Chang RK, Guo X, Burnside BA, Cough RA. Fast dissolving tablets. Pharm Tech, 2000; 24, 52-58.

[6] Dixit, S., et al., Fast Dissolving Tablet-A Promising Approach For Drug Delivery: A Review. Journal of Pharmacy Research, 2012; 5(3) 1508-1513.

[7] Modi A and Tayade P. Enhancement of dissolution profile by solid dispersion(kneading) technique. AAPS Pharm. Sci. Tech, 2006; 7(3) 68-75.

[8] Prabhakar. V et al., Fast Dissolving Tablets: An Overview. International Journal of Pharmaceutical Sciences : Review and Research, 2012;16(1) 17-26.

[9] Rajeev Soni. et al., Design And Development Of Quick Dissolving Tablet Containing Loratadine By Direct Compression Method.IJPCBS, 2013; 3(3) 771-800.

[10] Sreenivas, S., et al., Orodispersible tablets: New-fangled drug delivery system-A review. Indian Journal of Pharmaceutical Education, 2005; 39(4) 177-185.

[11] Tran P, Pyo YC, Kim DH, Lee SE, Kim JK, Park JS. Overview of the Manufacturing Methods of Solid Dispersion Technology for Improving the Solubility of Poorly Water-Soluble Drugs and Application to Anticancer Drugs. *Pharmaceutics*. 2019;11(3):132. Published 2019 Mar 19.

[12] Gauri, S. and G. Kumar, Fast dissolving drug delivery and its technologies. The pharma innovation, 2012; 1(2) 34-39.