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IMPROVEMENT OF SOLUBILITY AND DISSOLUTION RATE OF CARVEDILOL BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity and it is indicated for the treatment of mild-to-severe chronic heart failure and hypertension. By preparing solid dispersion of Carvedilol with poloxamer 188 and PVP K90 solubility of Carvedilol was significantly improved. Solid dispersion can be prepared in different ratios such as 1:1, 1:2, and 1:4. This prepared solid dispersion evaluated for drug content, solubility study and dissolution study. The drug content of different batches such as A1 is 78.99 %, A2 is 91.19%, A4 is 93.03%, B1 is 93.60%, B2 is 94.71% and B4 is 99.34 % respectively The solid dispersion technique with PVP K90 as a carrier provides a promising way to not only enhance the solubility but also dissolution rate of carvedilol.Tablet prepared by using sodium starch glycolate in 4% concentration shows 100% drug release in 30 min as compared to the tablets which can be prepared without superdisintegrants. After stability study of immediate release tablet there was no significant changes can be observed in Hardness, disintegration and % release of drug. It indicates that the prepared tablet is stable throughout the study.

KEYWORDS: Carvedilol, PVP K90, Poloxamer 188, Solid dispersions, Solubility, Dissolution rate, etc.

INTRODUCTION

Drug absorption from the gastrointestinal tract can be limited by a variety of factors, most significant contributors being poor aqueous solubility and poor membrane permeability of the drug molecule. When delivering an active agent orally it must first dissolve in gastric and or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Hence, two areas of pharmaceutics research that focus on improving the oral bioavailability of active agents include; enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly water soluble drugs.[1-3]

Carvedilol is a novel, multiple-action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. The reduction in blood pressure, produced by carvedilol, results primarily from beta-adrenoceptor blockade and vasodilation, the latter resulting from alpha 1-adrenoceptor blockade. Being categorized as class II compound as per the BCS classification system, it possesses very poor bioavailability and shows significant first pass metabolism.[1] Moreover, it is desirable to improve the solubility as well as bioavailability of carvedilol. The most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier. The incorporation of drug into solid carriers has been reported to result in an increase in the dissolution of drug leading to improved bioavailability.

The term solid dispersion refers to a group of solid products consisting of a hydrophilic matrix and a hydrophobic drug. The matrix can be amorphous or crystalline in nature.[4-5] Solid dispersions have been extensively studied for improvement of dissolution rate and numerous techniques of diverse nature have been developed for preparation of the same. Because of the simplicity of manufacturing and scale up processes, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared by using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatine encapsulation.[6] Single or combination of carriers may also be essential for development of solid dispersion.

MATERIALS AND METHOD

Materials

Carvedilol was provided by Alkem laboratories Ltd, Mumbai., India as a gift sample and PVP K90 and Poloxamer 188 were purchased from Alkems labs Ltd,

Mumbai and Signet chemical corporation Pvt Ltd, Mumbai, India. All other chemicals and reagents used were of desired analytical grade.

Methods

Preparation of solid dispersion by Kneading Method

Drug (Carvedilol) and hydrophilic polymers were triturated in a mortar with a small volume of a solvent blend of water: methanol (1:1). The thick slurry formed was Kneaded for 45 min and then dried at 55ºC until dry. The dried mass was powdered and sieved through mesh No. 120.[7]

Table no. 1: Composition of solid dispersion.

Sr. No.	Formulation code	Composition	Drug :polymer ratio
1	A1	Carvedilol+ PVP K90	1:1
3	A2	Carvedilol+ PVP K90	1:2
3	A4	Carvedilol+ PVP K90	1:4
4	B1	Carvedilol + polo 188	1:1
5	B2	Carvedilol + polo 188	1:2
6	B4	Carvedilol + polo 188	1:4

Solubility studies of Carvedilol solid dispersion

Solubility measurements of Carvedilol were performed according to a published method. Solid dispersions equivalent to 100 mg of Carvedilol was shaken with 10ml distilled water in stopper conical flask in an orbital shaker for 24 hours at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper no 1. Filtered solution was diluted properly with 0.1N HCl. The diluted solution was analyzed for the Carvedilol in UV at 241 nm.[8-9]

Drug content

Solid dispersions equivalent to 10 mg of Carvedilol were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 241 nm by UV spectrophotometer. The Actual Drug Content was calculated using the following equation as follows:[10-11]

%Drug content = (Mact/M_t) X 100

Mact = Actual amount of drug in Solid dispersion
Mt = Theoretical amount of drug in solid dispersion

Dissolution study

The dissolution rate of Carvedilol as such and from solid dispersions prepared was studied respectively in 900 ml of 0.1 N HCl using USP type II (paddle type) dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±5°C was maintained throughout the study. Drug or solid dispersion equivalent to 25 mg of Carvedilol was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed at 241 nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid.

Preparation of immediate release tablet from solid dispersion

The best batch of solid dispersion of Carvedilol (B4) was chosen and formulated into immediate release tablet. Formulations can be prepared by using superdisintegrants and other excipients such as magnesium stearate, talc, and microcrystalline cellulose for solid dispersed Carvedilol. Immediate release tablets can be prepared by direct compression method. Required quantities of solid dispersion (equivalent to 25 mg of Carvedilol) filler, and other excipients were blended together for some time (10 min) after passing all the materials through 60 mesh screen and mixed with magnesium stearate and talc. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 300 mg using concave punch of size 7mm.[12-15]

Table no. 2: Formulation of tablet.

Sr. No.	Ingredients	F1	F2
1	Solid dispersion (equivalent to 25 mg of Carvedilol)	125	125
2	Microcrystalline Cellulose	169	157
3	Magnesium stearate	3	3
4	Talc	3	3
5	Sodium starch glycolate	-	12
6	**Total**	**300 mg**	**300 mg**

Drug-excipients compatibility study

To study the interaction between drug and polymers used in the preparation of solid dispersion. FTIR spectrum of pure Carvedilol, polymer and physical mixtures were recorded. The drug and polymers separately and in combination with each other were mixed with KBr plate for determination of spectrum. The range selected was from 600cm-1 to 3800cm-1.[16-19]

RESULT AND DISCUSSION

Fourier transforms infrared spectroscopy

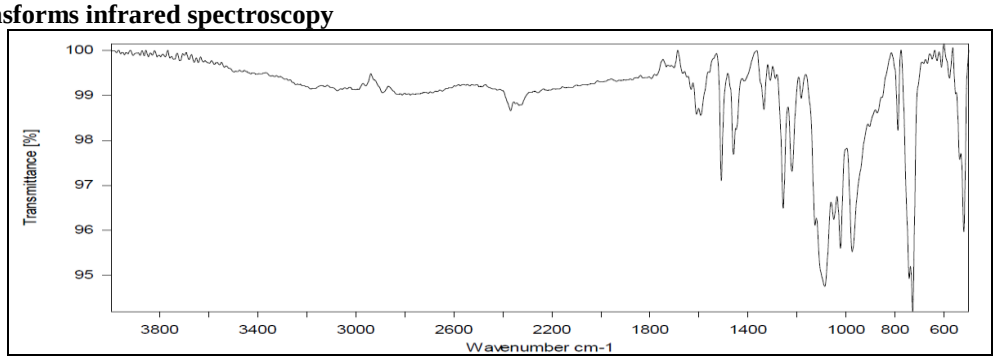

Figure 1: IR Spectra of Carvedilol.

FTIR of pure Carvedilol shows characteristics bands belonging to carbazol moiety at 1100, 1500, 2900 Cm $^{-1}$ corresponding to aromatic secondary C-N vibrations, C=C multiple bonds stretching, and C-H stretching of aromatic ring respectively.

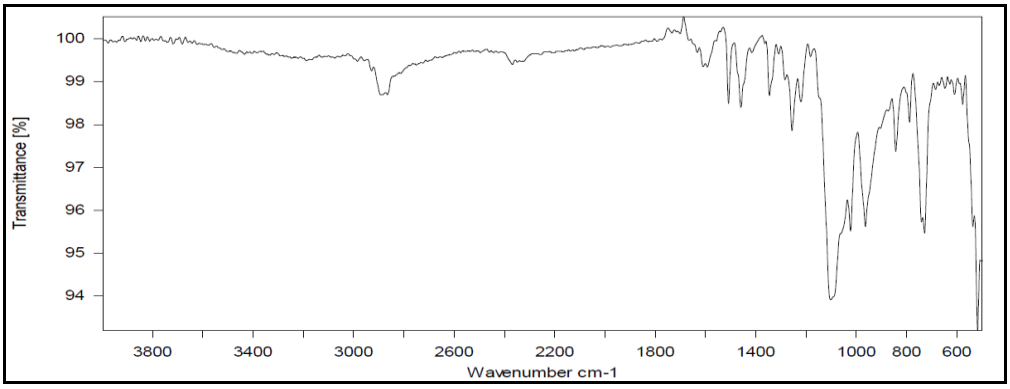

Figure 2: IR spectra of physical mixture of Carvedilol and poloxamer 188.

FTIR of pure Carvedilol shows characteristics bands belonging to Carbazol moiety at 1100, 1500, 2900 Cm -1 corresponding to aromatic secondary C-N vibrations, C=C multiple bonds stretching, and C-H stretching of aromatic ring respectively. FTIR-spectra of drug and its physical mixture with polymers are exactly same, and there is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients.

Formulation Plan of Carvedilol Solid Dispersion

Carvedilol solid dispersion can be formed by using the drug and polymer at different ratio. In the present study solid dispersion of Carvedilol can be formed by using PVP K90 and poloxamer 188.By using PVP K90 and poloxamer 188 solid dispersion can be formed by different ratio such as 1:1, 1:2 and 1:4 ratio.

Characterization of Solid Dispersion

Solid dispersion prepared by kneading method was evaluated for their flow properties such as Bulk density, Tapped density, Compressibility index, Hausner's ratio, and angle of repose. The Bulk density of solid dispersion was found to be 0.782 gm/cm^3 to 0.087 gm/cm^3. The Tapped density of solid dispersion was found to be 0.939 ± 0.052 gm/cm^3 to 1.073 ± 0.06 gm/cm^3.the Compressibility index of solid dispersion was found to be 17.61 ± 6.51 % to 24.98 ± 5.95%. The Hausner's ratio for solid dispersion was varied from 1.19 ± 0.04 to 1.32. The angle of repose for solid dispersion was varied from 37.31 and 39.11.

Table no. 3: Characterization of solid dispersion.

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (CI) (%)	Hausner's ratio	Angle of repose (θ)
A1	0.087±0.03	1.073 ± 0.06	20.09 ± 4.22	1.19 ± 0.04	37.31 ± 2.194
A2	0.81 ± 0.03	1.00 ± 0.09	17.61 ± 6.51	1.21 ± 0.10	37.10 ± 4.60
A4	0.81 ± 0.06	1.09 ± 0.171	24.67 ± 5.95	1.32 ± 0.10	38.53 ± 1.005
B1	0.768 ±0.04	0.939 ± 0.052	18.95 ±3.15	1.26 ± 0.01	38.25 ± 2.494
B2	0.782 ± 0.112	0.950 ± 0.14	24.98 ± 5.38	1.30 ± 0.03	37.22 ± 0.629
B4	0.83 ± 0.03	1.09 ± 0.03	23.48 ± 1.64	1.30 ± 0.03	39.11 ± 1.005

n=3

Solubility study of Carvedilol solid dispersion

Solubility study of solid dispersion as well as pure drug can be performed. The solubility of pure drug (A) is 18mg/ml, whereas the solubility of batch (A1) which contain Carvedilol and PVP K90 (1:1 ratio) is 24.50mg/ml. Batch (A2) which contain Carvedilol and PVP K90 (1:2 ratio) is 30.14mg/ml. And Batch (A4) which contain Carvedilol and PVP K90 (1:4 ratio) is 50.14mg/ml. The solubility of batch (B1) which contain Carvedilol and poloxamer 188 (1:1 ratio) is 41.50 mg/ml. Batch (B2) which contain Carvedilol and poloxamer 188 (1:2) ratio is 51.26 mg/ml. Batch (B4) which contain Carvedilol and poloxamer 188 (1:4 ratio) is 61.12 mg/ml. The optimized batch is B4 which shows high solubility as compared to other batches. The increase in solubility with increasing poloxamer concentration indicates the solvent properties of the poloxamer 188 for the drug. Poloxamer 188 causes decrease interfacial tension between the drug and dissolution medium. These results could be explained that reduction in crystallinity of the drug lead to decrease of the energy required for the dissolving process and also to a highly dispersed state of the drug.

Table no. 4: Solubility study of solid dispersion.

Sr. No.	Formulation code	Drug : carrier ratio	Solubility mg/ml
1	A	Pure drug	18
2	A1	Carvedilol+ PVP K90(1:1)	24.50
3	A2	Carvedilol+ PVP K90(1:2)	30.14
4	A4	Carvedilol+ PVP K90(1:4)	50.14
5	B1	Carvedilol + poloxamer 188(1:1)	41.50
6	B2	Carvedilol + poloxamer 188 (1:2)	51.26
7	B4	Carvedilol + poloxamer 188 (1:4)	61.12

Drug content of solid dispersion

Solid dispersion prepared by kneading method were evaluated for drug content, drug content of all the solid dispersion is in the acceptable range. The drug content of different batches such as A1 is 78.99 %, A2 is 91.19%, A4 is 93.03%, B1 is 93.60%, B2 is 94.71% and B4 is 99.34 % drug content respectively. The optimized batch is B4 which shows high drug content as compared to other batches.

Table no. 5: Drug content of solid dispersion.

Sr. No.	Formulation code	Drug : carrier ratio	% Drug content
1	A1	Carvedilol+ PVP K90(1:1)	92.44
2	A2	Carvedilol+ PVP K90(1:2)	91.19
3	A4	Carvedilol+ PVP K90(1:4)	93.03
4	B1	Carvedilol + poloxa 188(1:1)	93.60
5	B2	Carvedilol + poloxa 188 (1:2)	94.71
6	B4	Carvedilol + poloxa 188 (1:4)	99.34

% Drug release from solid dispersion

The drug release profile for all formulations was shown in table.3 The drug release of PVP K90 and poloxamer 188 at 1:1, 1:2, and 1:4 ratio gives 80.177, 86.760, 91.932, 89.58, 94.753, and 99.935% respectively. The optimized batch is B4 which contain poloxamer 188 and Carvedilol at 1:4 ratios which give 99.925% drug release in 60 min as compared to PVP K90 which give only 91.932% drug release in 60 min. As we increase the concentration of polymer increases the dissolution rate of the drug.

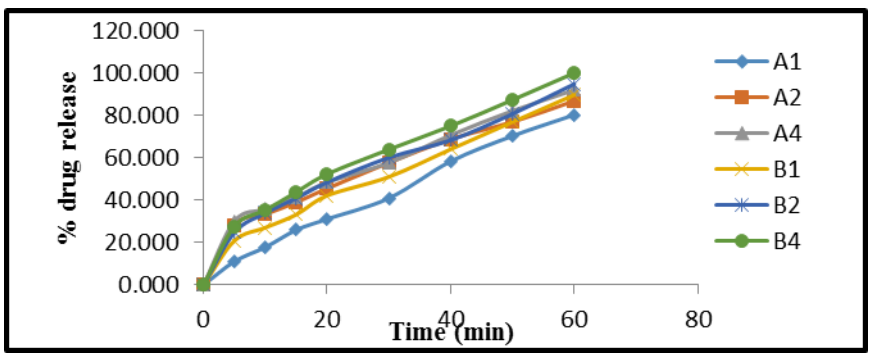

Figure 3: % Drug release from solid dispersion

Evaluation of Tablet

The hardness of the tablets prepared by direct compression methods was determined by Pfizer tester and found to be within the range of 4.38± 0.02 kg/cm^2 to 4.53 ± 0.03 kg/cm^2. The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 4.33 ± 0.02mm to 4.53 ± 0.03 mm. The standard deviation values indicated that all the formulations were within the range. The % friability of tablet was determined by using Roche friabilator. % friability is in the range of 0.51 to 0.53%. All the formulations showed % friability less than 1% that indicates ability of tablets to withstand shocks abrasion during the transportation and packing hazards. The weight variation was found in all designed formulations in the range 298 ± 8.091 to 302 ± 6.318 mg. Rapid disintegration within 2 to 4 minute was observed in all the formulations.

Table no. 6: Evaluation of tablet.

Formulation code	Hardness Kg/ cm2	Thickness (mm)	Friability (%)	Weight variation	Disintegration time (min)
F1	4.38±0.2	4.33±0.02	0.51±0.06	298±8.091	4.02 ± 0.02
F2	4.53±0.03	4.53±0.03	0.53±0.06	302±6.318	2.01 ± 0.02

n=3

% Release of drug from tablet

Tablets which can be prepared from optimized batch of solid dispersion (B4) by direct compression were studied for % release of drug. Two batches of the tablet can be prepared such as F1 and F2 by using superdisintegrants such as sodium starch glycolate in 4% concentration. Batch F1 is prepared without superdisintegrants and batch F2 is prepared with superdisintegrants. Tablet which can be prepared without superdisintegrants shows 98.985% drug release in 60 min whereas tablet which can be prepared with superdisintegrants shows 100 % drug release in 30 min.

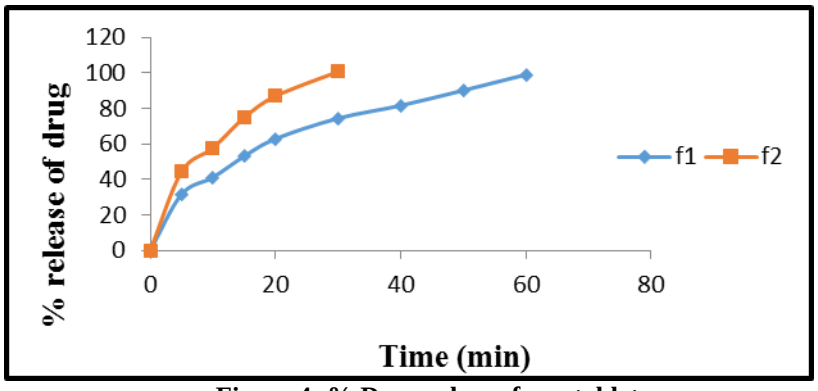

Figure 4: % Drug release from tablet.

Stability Study of Optimized Solid Dispersion

% drug release from solid dispersion after stability study

Stability studies were carried out at 40 ± 0.2 ºC and relative humidity 75 ± 5% for 30 days and these formulations are able to remain their stability for one month in a stability chamber. The optimized solid dispersions were stable for one month and no significant changes were observed in % release of drug from solid dispersion after stability study.

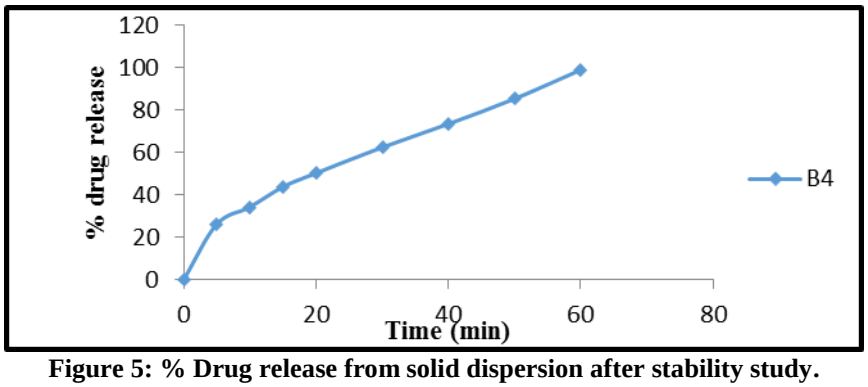

Figure 5: % Drug release from solid dispersion after stability study.

Drug content

Stability studies were carried out at 40 ± 0.2 ºC and relative humidity 75 ± 5% for 30 days and these formulations are able to remain their stability for one month in a stability chamber. The optimized solid dispersions were stable for one month and no significant changes were observed in % drug content from solid dispersion after stability study.

Stability Study of Immediate Release Tablet

% Drug release from Tablet after stability study

Stability studies were carried out at 40 ± 0.2 ºC and relative humidity 75 ± 5% for 30 days and these formulations are able to remain their stability for one month in a stability chamber. The optimized batch of immediate release tablet stable for one month and no significant changes were observed.

Table no. 7: Evaluation of tablet after stability study.

Stability data	Formulation code	Hardness (Kg/ cm^2)	Disintegration time (min)
Before stability	F2	4.53 ± 0.03	2.01 ± 0.02
After stability	F2	4.06 ± 0.05	2.00 ± 0.01

CONCLUSION

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity and it is indicated for the treatment of mild-to-severe chronic heart failure and hypertension. Its biological half-life is very short (7-10 hrs) and it is 90% absorbed from GIT, but its bioavailability is very low (25-35%) therefore it is an ideal drug candidate for improvement of solubility and dissolution rate and ultimately preparation of fast dissolving drug delivery system. By preparing solid dispersion of Carvedilol with poloxamer 188 and PVP K90 solubility of Carvedilol was significantly improved. Sold dispersion can be prepared in different ratios such as 1:1, 1:2, and 1:4. This prepared solid dispersion can be evaluated for drug content, solubility study and dissolution study.

REFERENCES

1. Rathore D., Thakur R., Narwal S., Solid dispersion a new horizon in novel drug delivery system. Journal of Pharmacy Research, 2012; 5(2): 1007-1014.
2. Jatwani S., Rana A., Singh G., and Aggarwal G., An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. International journal of pharmaceutical sciences and research, 2012; 3(4): 943.
3. Tyagi R., Dhillon V., Solid dispersion a fruitful approach for improving the solubility and dissolution rate of poorly soluble drugs. Journal of Drug Delivery & Therapeutics, 2012; 2(4): 6-7.
4. Annamma Devi G., Vijaya Ratna J., Sywalini V., Akshara T., Effect of hydrophilic polymers on solid dispersions of Carvedilol for enhancing its dissolution rate. Journal of Global Trends in Pharmaceutical Sciences, 2012; 3(2): 708-713.
5. Tekade, B.W. Jadhao U. T. Thakare V. M., Formulation and evaluation of diclofenac sodium effervescent tablet. IPP, 2014; 2(2): 350-358.
6. Kolasinaca N., Kachrimanisc K., Homseka I., Grujica B., Đuricb Z., Ibri S., Solubility enhancement of Desloratadine by solid dispersion in Poloxamers. *International Journal of Pharmaceutics, 2012;* 436: 161– 170.
7. Annamma Devi G., Vijaya Ratna J., Sywalini V., Akshara T., Effect of hydrophilic polymers on solid dispersions of Carvedilol for enhancing its dissolution rate. Journal of Global Trends in Pharmaceutical Sciences, 2012; 3(2): 708-713.
8. Srinivasa Rao Y., Vijaya L., Chandana R., and Chowdary KPR. Formulation and Evaluation of Carvedilol Solid Dispersions for Dissolution Rate Enhancement. International Journal of Advances in Pharmacy, *Biology and Chemistry*, 2012; 1(4): 489-495.
9. Thakare V. M., Tekade, B.W. Development of metoclopramide hydrochloride oro-dispersibal tablets using taste masking tulsion 339. J. Adv. Pharm. Edu. & Res, 2013; 3(4): 480-486.
10. N.G.R. Rao, T. Patel,S.Gandhi. Development and evaluation of carbamazepine fast dissolving tablets prepared with a complex by direct compression technique.Asian journal of pharmaceutics, 2009; 97-103.
11. Tanvir J. Shaikh., et.al. Formulation and development of orodispersible tablets of lornoxicam by using resinate inclusion complexes. IPP, 2017; 5(2): 103-111.
12. Thorat Y., Gonjari I., and Hosmani A., solubility enhancement techniques: A review on conventional and novel approaches. International journal of pharmaceutical sciences and research, 2011; 2(10): 2501-2513.
13. Chowdary K., Achanta P., Teja R., and Krishna M., A Factorial Study on the Enhancement of Dissolution Rate of Aceclofenac by Solid Dispersion in Combined Carriers. Pharmacie globale International journal of comprehensive pharmacy, 2012; 7(04): 1-2.
14. V. M. Thakare et al.: Development of Metoclopramide Hydrochloride Orodispersibal tablets using taste masking tulsion., Journal of Advanced Pharmacy Education & Research, 2013; 3(4): 480-486.
15. Benker, G.S., Anderson, N.R., Tablets. In: Lachman, L., Lieberman, H.A., Kanig, J.L., The theory and practice of industrial pharmacy, 3rd ed. Varghese Publishing House, 1987; 300.

16. USP/NF. Physical Tests: Bulk density, Tapped density, Flow properties,Disintegration, Dissolution. 22/17 ed. Rockville MD.: United States Pharmacopeial Convention Inc, 1995; 2049-2050.
17. Patil A. et.al., Formulation And Evaluation Of Stable Oral Formulation Of Bitterless Ofloxacin complexes with Ion Exchange Resin, World Journal Of Pharmaceutical Sciences, 2012; 1(1): 384-386.
18. Rashmi D. And Sharma R; Formulation And In vitro Evaluation Of Taste Masked Orodispersible Tablet of Metoclopramide Hydrochloride Using Indion 204, International Journal of Chem Tech Research, 2010; 2(1): 448-451.
19. Watson, D.G., Pharmaceutical Analysis A textbook for pharmacy students and pharmaceutical chemists, first ed. London, Churchill Livingstone, 1999; Pp.100-03.
20. Duerst, M., Spectroscopic methods of analysis: infrared spectroscopy. In: Swarbrick J., Boylon J.C., Encyclopedia of Pharmaceutical Technology. 3rd Ed. vol. 5. Marcel Dekker Inc. New York, 2007; pp. 3405- 3418.
21. Skoog, D.A., Holler, F.J., Nieman, T.A., Principles of Instrumental Analysis. 5 th ed. Sounder's College Publishing, 2004; pp. 798- 808.