EFFECT OF SOLUBILIZATION TECHNIQUE ON DISSOLUTION

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More than 40 percent of newly discovered drugs have little or no water solubility thus the present research aimed at the study of improvement of solublisation on dissolution by addition of different solublising agents and modification of methods. Irbesartan is the drug of choice. Effect of Solubility on dissolution was studied with some solubilizing agents like β-Cyclodextrins, PEG-6000, Polysorbate-80, Cremophore and Resins (Doshion). It was seen that Irbesartan give 90 percent release in 1hr with polysorbate-80 where cremophore containing tablets showed 97 % release in 1 hr in case of solid dispersion technique and in case of complexation technique respectively. Thus the present study concluded that, dissolution rate of poorly soluble drug can be increases by using solubilizing agent as well as using different techniques.

Key words: Solubilization, Irbesartan, Resins, Complexation

INTRODUCTION

Irbesartan is used as angiotensin II receptor antagonists[1] having the chemical formula 2-butyl-3-[{2'- (1H-tetrazol-5-yl) {1, 1'- biphenyl}-4-yl} methyl} -1, 3-diaza- spiro (4, 4) non-1-en-4-one[2]. The reason behind this study is more than 40% of newly discovered drugs have little or no water solubility; presently it is a serious challenge to the successful development and commercialization of new drugs in the pharmaceutical industry. More than 90% of drugs approved since 1995 have poor aqueous solubility, poor membrane permeability or both[5]. Approximately 16% has less than optimal performance specifically because of poor solubility and low bioavailability. A marketed drug with poor water solubility can still show performance limitations such as incomplete or erratic absorption[6], poor bioavailability, and slow onset of action. Effectiveness can vary from patient to patient, and there can be a strong effect of food on drug absorption.

Finally, it may be necessary to increase the dose of a poorly soluble drug to obtain the efficacy required. Although pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs, those have aqueous solubility of less than 0.1 mg/ml[6]. Irbesartan is the drug having less water solubility and solubility of this drug can be improve by addition of solubilizing agents[7] as well as using various solubilization techniques like Solid dispersion[8-10], Complexation[11-12], Self Microemulsifying[13] and cosolvency[14].

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MATERIAL AND METHODS

Irbesartan was gift sample of Matrix Labs, β-Cyclodextrins was supplied by Biocon Ltd, PEG-6000 Visas chemicals limited, Polysorbate-80 from loba chem, Cremophore from ISP surfactant and Resins(doshion) from Doshi Ion exchange and chemical, microcrystalline cellulose from FMC Biopolymer, crospovidone from ISP technologies.

Preparation of granules

Measured amount of Irbesertan are mixed with the diluents mentioned in table I for preparation of tablet with wet granulation technique taking pregelatinised starch as a binder. Solid mass was passing through 22 mesh size and dried under hot air oven for preparation of granules. After preparation of granules, preformulation study was carried out. Data are shown in table II.

Bulk Density:

First, 10 g of API (active pharmaceutical ingredient) was weighed accurately and kept in a cleaned dried graduated measuring cylinder. Then after pouring the granules into the measuring cylinder granule bed made

uniform without disturbing much. Then the volume was measured directly from the graduation marks as ml or cc. The volume measure is called is the bulk volume and the bulk density is calculated by the following formula-

$$Bulk\ density = \frac{weight\ of\ granules}{bulk\ volume}$$

Tapped density:

After measuring the bulk volume, the same measuring cylinder was subjected to 500 & 1250 mechanical taps with the help of a mechanical tapping machine (tapped density measuring apparatus). After tapping, the volume was again measured as ml or cc, which is called as tapped volume and the tapped density is calculated by the following formula-

$$Tapped\ density = \frac{weight\ of\ granules}{tapped\ volume}$$

Carr's Compressibility Index

It is one of the most important parameter to characterize the nature of powders and granules. It can be calculated from the following equation

$$Compressibility\ Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density}$$

Hausner's Ratio: Hausner's ratio is an important character to determine the flow property of powders and granules. This can be calculated by the following formula

$$Hausner's\ ratio = \frac{Tapped\ desity}{Bulk\ denstiy}$$

Particle size determination (Sieve analysis): An accurately weighed (10 g) quantity of pure drug was passed through a series of the sieves i.e.25, 30, 35, 45, 60, 80, and 100,200 with the help of sieve shaker. Then the sieves are removed from the sieve shaker and the powder retained in each sieve was collected and weighed and percentage of powder retained on each sieve was calculated using the initial weight taken.

Solubility determination in different media:

A quantitative determination of solubility was done by preparing saturated solutions of drug in different medium i.e. 0.1 N HCL, water, pH 6.8, 6.5 and 7.5 Phosphate buffer, pH 4.5 acetate buffer respectively by adding excess amount of drug into the media and placed in a sonicator for 2 hours. The resultant solution were filtered, diluted and checked for absorbance at the respective medium blank and comparing the absorbance, amount of drug was determined.

Preparation of tablet

After preparation of Irbesartan granules are ready for preparation for tablet compression. Finally magnesium stearate is mixed with irbesertan granules which are used as a lubricating agent just prior to tablet punch. Tablets were manufactured as per the formula given in table I using 8 station tablet compression machine (cadmach).

In process Test

Compressed tablet may be characterized by a number of specifications given in table I such as size, shape, thickness, hardness, friability, weight, and disintegration time.

Weight variation

After the tablet machine is in operation, the weights of tablets are checked routinely to ensure the proper weights of tablet are being made. 20 tablets were taken each time and weighed accurately to determine the weight variation.

Hardness

Hardness determination are made a throughout the tablet runs to determine the need for pressure adjustment on the tablet compression machine. 5 tablets are taken for checking the hardness test. The average was calculated after performing the hardness test with Dr. Schleiunger.

Friability

20 tablets are taken doing the friability using Roche's friabilator for 4mins at 25rpm. Friability was calculated by using the formula-

$$\%\ Friability = \left(\frac{W_0 - W}{W_0}\right) \times 100$$

Where, W_0 = Weight of tablets before rotation

W= Weight of tablets after rotation

Table I: Composition of different tablet containing irbesartan, valsartan and telmisartan

Ingredients	F_T	F_1	F_2	F_3	F_4	F5	F6
Irbesartan	300	300	300	300	300	300	300
LM	120	268	258		258	258	258
MCC	85.5						
PgS	60						
Aerosil 200	6						
CCS	24	28	28	12	28	28	28
MgS	4.5	4	4	4	4	4	4
PEG-6000			10				
βCD				254			
Polysorbate 80					10		
Cremophore						10	
Resins (Doshion)							10

LM- Lactose Monohydrate, MCC- Microcrystalinecellulose, PgS- Pregelatinized starch,
CCS- Crosscarmilose sodium, MgS- Magnesium stearate, PEG- Polyethylene glycol,
CD- Cyclodextrine, DCP- Dibasic calcium phosphate

Disintegration time

Uncoated tablets should be disintegrating within Indian Pharmacopoeia limit in water at 37 °C using I.P. disintegration test apparatus.

Thickness

Thickness of the tablet is controlled during production and it was determined by vernier caliper in mm.

Dissolution Studies

The dissolution was assessed using standard USP Apparatus II in 900ml of 0.1 N HCl. The stirring speed was 100 rpm. Total 3 tablets of each formulation were taken for release study. Temperature was maintained at 37 ± 0.5º C throughout the experiment. Dissolution study was carried out for 60 min with sampling intervals of 5, 10, 15, 30, 45 and 60 mins. After collection of sample in each interval, dissolution medium was replenished with the same volume of media. In each sampling time 10ml was pipette out and filtered through 0.45± 0.1 mm diameter filter paper and analyzed for the % drug release in U.V. spectrophotometer at 259 mm.[15]

RESULTS AND DISCUSSION

The present research aimed at the study of improvement of solublisation on dissolution by addition of different solublising agents and modification of methods. Effect of Solubility on dissolution was studied with some solubilizing agents like β-Cyclodextrins, PEG-6000, Polysorbate-80, Cremophore and Resins (Doshion). Tablets are prepared as per formula mentioned in table I. Before tablet compression, a preformulation study was carried out. It was seen that, all the parameter like bulk density, Tapped density, Compressibility index and Hausner's ratio are in their concentration range as per standard reference books and journals. The outcomes were as per expectation and results were satisfactory shown in table II. After comparing physical parameter of all tablets, it was seen that F1, F2 and F6 have low hardness, friability and thickness as compare to others except disintegration time shown in table II.

The processes such as micronisation, jet milling, spray drying and freeze drying are not applied due to fineness nature of all API. Solid dispersion, complexation are most common method for solubility enhancement. With surfactants such as polysorbate-80, cremophore has also

great effect on dissolution. Solid dispersion with PEG-6000 is a critical process for solubility. In case of F3, F4 and F5 showed the better dissolution results observed in case of adding polysorbate-80 upto 90% in 1hr. shown in Figure I. Other processes are not so acceptable due to its poor release rate.

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration, (2) Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. From the release kinetics it was seen that the r^2 (table II) value of zero order kinetics is not linear when compare with Higuchi's plot. The r^2 value was between the ranges 0.743 to 0.955 which much linear with regression coefficient that means the release of drug from the formulation was diffusion controlled.[16]

Table II: Parameter of drugs and in process quality control test of tablets

Parameters	**Specification**	**Irbesartan**
Appearance	Crystalline	Crystalline
Melting Point (ºC)	100-300	428-429.5
	Solubility mg/ml	
0.1N HCl	0.5	0.354
Water	0.5	0.579
pH 4.6 acetate buffer	0.5	0.798
pH 6.5 phosphate buffer	0.5	0.721
pH 6.8 phosphate buffer	0.5	------
pH 7.5 phosphate buffer	0.5	------
Bulk density (gm/ml)	0.3	0.2
Tapped density (gm/ml)	0.3	0.28
Compressibility index	30	28.5
Hausner's ratio	2	1.4
Weight (mg)	600	600
Hardness (kg/cm2)	5-15	10.8
Friability (%)	0.2	0.2
Thickness (mm)	5.15±0.15	5.15
Disintegration (min)	Within 15min	2.45
Punch detail (mm)	17.1×9.15	17.1×9.15
Release kinetics	**Zero order**	**Higuchi's plot**
Ft	R^2=0.393	R^2=0.839
F1	R^2=0.535	R^2=0.921
F2	R^2=0.468	R^2=0.888
F3	R^2=0.391	R^2=0.743
F4	R^2=0.338	R^2=0.565
F5	R^2=0.322	R^2=0.541
F6	R^2=0.530	R^2=0.955

CONCLUSION

The present research aimed at the study of improvement of solubility on dissolution by addition of different solublising agents and modification of methods. Some of the solubilizing agents were showed satisfactory result on dissolution. From the present study, it can be concluded that solid dispersion and complexation method can be used for increasing the solubility of poorly soluble drugs with addition of solubilizing agents.

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REFERENCES

1. Hoogerwerf WA, Pasricha PJ. Agent used for control of gastric acidity and treatment of peptic ulcers and gastroesophageal reflux disease. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 9th ed. International Publication McGraw Hill; 1996. P. 1007-1009
2. Shah JC, Chen JR, Chow D. Preformulation study of etoposide: II. Increased solubility and dissolution rate by solid-solid dispersions. Int. J Pharm. 1995; 113: 103-11.
3. Raju YP, Garbhapu A, Prasanna SAL, Rao BS, Murthy KVR. Studies on enhancement of dissolution rate of etoposide. Indian J pharm sci. 2007; 69(2): 269-73.
4. Chang SL, Chen GL, Gandhi GH. Enhancement of dissolution rate of valdecoxib with solid Dispersion using PEG-4000. Drug development industrial pharmacy. 2005; 31: 349-357.
5. Roa MG, Sfu'11eetha R, Sullukarreddy P,Ravi JK. Preparation and evaluation of solid dispersion of Naproxen. Drug dcvelopment Industrial Pharmacy. 2005; 30: 27-29.
6. Prabhu S, Brocks DR, Behageri GV. Enhancement on dissolution of ethopreperazine using solid dispersion of ethoproperazine solid dispersion prepared with phospholipid and/or PEG. Drug development Industrial Pharmacy. 2001; 31: 413-419.
7. Feng C, Jinaxin G, Queng P. Physico-chemical characteristics of freeze dried sculetarrin cyclo dextrin tetra component complex. Drug development Industrial pharmacy. 2005; 30: 747-754.
8. Nagarsenkar MS, Joshi MS. Celecoxich-cyclodextrin systems. Characterzation and evaluation in-vitro and in-vivo adsorption. Drug development Industrial pharmacy. 2005; 31: 169-179.
9. Cui S, Zhao C, He Z. Self microemulsfiying drug delivery system for improving in-vitro dissolution and oral absorption of pueraria Lobata isoflavonel. Drug development Industrial pharmacy. 2005; 31: 349-357.
10. Modi A, Tayade P. A comparative solubility enhancement profile of valdecoxib with different solubilization approaches. Indian j pharm sci. 2007; 69(2): 274-78.
11. Das S, Bhuyan NR, Chanda R, Bahadur S, Choudhury A, Saha S. Preparation and Evaluation of Mucoadhesive tablet of omeprazoole for Oral Controlled Release. Research Journal of Pharmacy and Technology. 2008; 01(03): 166-70.
12. Shoaib MH, Tazeen J, Marchant H A, Yousuf RI. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. Pak J pharm sci. 2005; 19(2): 119-24.

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