International Journal of Science Academic Research
Vol. 05, Issue 08, pp.8099-8110, August, 2024
Available online at http://www.scienceijsar.com

ISSN: 2582-6425

Research Article

FORMULATION AND CHARACTERIZATION OF BLONANSERIN TABLET USING LIQUISOLID TECHNIQUES

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Received 24th June 2024; **Accepted** 27th July 2024; **Published online** 30th August 2024

Abstract

Blonanserin use to treat Schizophrenia and other bipolar disorder. It is BCS II drug having low solubility. The affinity of Blonanserin for D_2 receptors is 20 and 94 fold higher than that of haloperidol and risperidone, respectively. Blonanserin has low affinity for 5-HT_{2C}, adrenergic α_1, histamine H_1, and muscarinic M_1 receptors which decrease certain adverse effects such as orthostatic hypotension, over sedation, weight gain, metabolic abnormalities, and peripheral anticholin ergic side effects. In this present research work blonanserin tablet was prepared using liquisolid techniques to increase solubility and bio availability of drug. Avicel ph 200 and Cab o sil was taken as carrier and coating material respectively. Blonanserin is more soluble in PEG 600 than other non volatile solvent. Optimization was done on the basis of 3^2 full factorial designs by taking different ratio of carrier and coating material to various drug concentrations in solvent. By the result it was observed that dissolution rate of blonanserin was significantly increase using this formulation.

Keywords: Liquisolid techniques, Blonanserin, Liquisolid tablet, Liquisolid compact.

INTRODUCTION

Introduction to drug delivery System

Basics of drug solubility [1,2,3]

The property of medicament solubility can plays an important role for their in vitro dissolution profile. Now a days the API are produced which are mainly lipophilic so they have less solubility. Scientist faces a challenge for development of this type of drug to be given as orally. As this type of route through mouth has been seen well patient convenient to than other routes, and cheaper in production for preparation of oral system. So as for a medicament to be enters into the blood circulation administration through the mouth cavity, the medicament follows the dissolution within the gastric fluids. The medicament which is use in the form of solid formulation should have been gone firstly absorption then inn to the blood circulation. For lipophilic medicaments, the rate of dissolution of this medicament plays an important role in rate limiting step as it correspondence to its absorption's degree and speed determination. Frequently many lipophilic medicaments exhibit very less or nearly to low absorption in colon part, as a result for this we can say, it is the very most difficult challenged to prepare tablets for this medicaments, it is said that the newly or recently formed drugs in which 1/3 parts of drugs are lipophilic. We scan sum up that half of the drug which have less than 50% solubility faces this type of problems associated with their high lipophilicity and low solubility. Bioavailability of this sparingly soluble medicament in water is stopped by their rate of dissolution and aqueous solubility. There are different kinds of option in which we can increase the dissolution rate by degrading its size of particle through preparing micro or nano formulation.

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Although, the small particle size medicaments have high efficiency to agglomerate thanks to hydrophobicity or van-der Waals attraction, which results in a downgrade in area beneath the time. Apart from this rate of dissolution can be enhance. With the help of this types of technique, the medicament is soluble in an organic solvent and then after by keeping of the solution by a silica like carrier which has high surface area. Here, agglomeration of the APIs particles is stopped thanks to the carrier. Although, thanks to the presence of the unwanted solvent beneath the preparation of medicaments, which is harmful to use in preparation of this system. From the centuries it had been taken care where different types of formulation or system are used to prepare and increase the dissolution rate of the drugs. Following are the method which can be use for this are given below

Approaches to reinforce dissolution of medicine[3,4]

- Pharmacokinetic approach: pharmacokinetic of APIs are altered e.g. pharmacokinetic is altered by changing its chemical structure.
- Pharmaceutical approach: Involves modification of pharmaceutical preparation. E.g. changing of formulation, manufacturing process.
- Biologic approach: Route of intake is changed e.g. oral to parental.
- Pharmaceutical approaches to reinforce dissolution of medicine.

1. **Use of surfactants:** Surface active excipients enhance dissolution rate by promoting wetting and penetration of dissolution aqueous thing into solid APIs particles example steroids like spironolactone.

2. **Micronization:** During which particle size of solid medicaments are reduced to 5 to 20 μ by spray drying or fluid energy mill example: sulpha drugs.

3. **Alteration of pH of the Drug Microenvironment:** It is obtained in two ways in keeping salt formation and

addition of buffers to the preparation e.g. Bufferin tablets.

4. **Salt forms:** Salts may be used to improved solubility and dissolution specification as compared to the first medicaments. Example salt of basic drug like Atropine is more soluble than parent medicaments.

5. **Metastable polymorphs:** Metastable polymorphs are often soluble than the stable polymorphs of medicaments that exhibits polymorphism, e.g. chloramphenicol palmitate.

6. **Solvent deposition:** In this method less aqueous soluble medicaments are dissolved in organic solvent and accumulated on an inert hydrophilic, solid matrix, e.g. nifedipine is dissolved in ethanol and accumulate in starch by evaporation of solvent.

7. **Selective adsorption on insoluble carriers:** A typically active adsorbent can increase the dissolution rate, e.g. bentonite.

8. **Solute –solvent complexation:** Solvates of medicaments with organic solvents mostly have higher aqueous solubility than the parent medicaments, e.g. 1:2 griseofulvin benzenesolvate.

9. **Solid solution:** Use of eutectic mixtures: These formulation also are formulate by fusion method it's gradually differ from primary solid solution as a result of fused melt of solute –solvent show complete miscibility but slightly less solid in solid solubility.

    - Use of solid dispersion: These are often formulated by solvent or co - precipitation system where both guest solute and therefore the solid carrier solvent are dissolved in common volatile liquid like methanol or ethanol. The liquid removed by evaporation under freeze drying or by reduced pressure which end in amorphous precipitation of guest in crystalline carrier.
    - Use of primary solid solution: solid solution is binary numeration system comprising of solid solute molecularly dispersed during a solid solvent.

10. **Molecular encapsulation with cyclodextrins:** The beta and gamma cyclodextrins and a variety of different their derivatives are unique in having the ability to prepare molecular inclusion with lipophilic drugs which having very less solubility in aqueous fluid. These cyclodextrin compounds are versatile in having a lipophilic cavity of size suitable that is often to accommodate water loving medicaments as a guest; the surface of the host molecule is comparatively water lovable. However, among them, the technique of ‘’liquisolid compacts” is one among the foremost promising technique. Thus, the molecularly encapsulated medicaments have greatly improved aqueous solubility and dissolution rate. Cheap, simple development technique and capacity of commercial production gives an advantage to this system.

Liquisolid Technique[11,12,13]

The very less rate of dissolution of aqueous insoluble medicaments remains a comparatively heavy problem in confronting the pharmaceutical industry. An emerging amount of latest and possibly drugs which are very effective chemical compounds don't reach the general public merely thanks to their very less amount of drugs exhibit in blood circulation due to inadequate dissolution in the body. Over the recent years, different solid dosage formulation systems, to reinforce the dissolution of sparingly soluble medicaments, are introduced with variety of results including success rate also. The formulation of liquisolid system may be a new and promising additional way towards such a completely unique aim. The active ingredient during a solid dosage form must undergo dissolution before it's available for absorption from the end of the colon. The less efficiency in the dissolution rate of characteristics of water-insoluble medicaments is a major challenge for pharmaceutical preparation for the scientists. The absorption rate of a sparingly aqueous soluble medicament, prepared as an orally administered solid dosage form, is controlled by its dissolution rate within the fluid present at the absorption site, i.e. the dissolution rate is usually the rate- determining step in drug absorption. Several researchers have shown that the liquisolid technique is that the most promising method for promoting dissolution rate of sparingly water soluble drugs.

The term liquisolid compacts as given by Spireas exhibit that immediate or sustained release system that are prepared using the method of “liquisolid systems” combined with inclusion of appropriate adjuvant needed for tabulating or encapsulation like preparation and for freely or sustained release action, like disintegrant or binders, respectively. It’s been observed that the APIs release superiority of liquisolid tablets is inversely proportional to the water solubility of the contained medicament. Liquisolid compacts formulated by using different solvents which dissolves the sparingly soluble medicaments and provides better bioavailability. Liquisolid system is novel technique developed by Spireas liquisolid preparation involves changing of liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent as this aqueous medication can be changed into free-flowing, dry looking, non-adherent, and readily compressible powders with the utilization of carrier and coating materials. Just in case of water-soluble medicaments, the sustained releases are often gettable. "Liquisolid systems" is formulated by changing liquid lipophilic medicaments, or medicament suspensions or solutions of water-insoluble solid medicaments in suitable non-volatile solvent systems, into "dry" (i.e., dry-looking), nonadherent, free-flowing and readily compressible powder blend by mixing with selected carrier and coating materials. On the basis of this reason liquid medication contained therein, liquisolid systems could also be classified into three subgroups:

- **Powdered liquid medicament.**

As the name defy the medicament in to a liquid form due to use of highly pressurized device it can be converter in to liquid form

The first two could also be produced from the conversion of API solutions or API suspensions and therefore the latter from the formulation of liquid medication into liquisolid system.

- **Powdered medicament suspensions**

In these formulations the drug is use as a small granules which has been powdered in to the low amount so that medicament can be make as a suspension form

- **Powdered medicament solution:**

Regarding "powdered drug solutions," it must be emphasized that their preparation isn't a solvent deposition preparation since it doesn't involve drying or evaporation. Since non-volatile solvents are wont to prepare the drug solution or suspension, the liquid vehicle doesn't evaporate and thus, the medicament is carried within the liquid system which high accuracy rate, is dispersed throughout the final formulation counting on the consistency of the powder blend, the amount of solid medicament dispersed within the aqueous fluid and therefore the physiochemical parameters of the liquid solvents used the suitable liquid-to-powder % ratios will range from 2% to 52%, the foremost preferable range being 10% to35%.

Aim and Objectives

Aim of investigation

Solubility of medicine could be a major consider the planning of pharmaceutical formulations result in variable oral bioavailability. Dissolution is a very important issue for absorption of medicine particularly just in case of water insoluble or poorly soluble medicine one. The rate limiting step for many of the Pharmaceutical formulations is dissolution. Varied ways used to increase the solubility of poorly water-soluble medicine are solid dispersions, inclusion complexes with β- cyclodextrins, micronisation, mixtures and spray drying technique. The new developed technique by Spiraeas, Liquisolid system improves the dissolution properties of water insoluble or poorly soluble medicine. The term 'Liquid-solid systems' (LS) is a pulverized kind of liquid drug developed by changing liquid oleophilic drug or drug suspension or resolution of water-insoluble solid drug in appropriate non-volatile solvent systems, into dry trying, non-adherent, free-flowing and readily compressible pulverized mixtures by mixing with selected carrier and coating materials. Various grades of cellulose, starch, lactose, etc. square measure used because the carriers, whereas terribly fine oxide powder is employed because the coating (or covering) material. The good flow and compression properties of Liquid-solid may be attributed because of massive area of oxide and fine particle size of avicel. Hence, Liquisolid compacts containing water-insoluble medicine expected to show enhanced dissolution characteristics and consequently improved oral bioavailability. The main aim of this study is to formulate Blonanserin tablets using liquid solid technique. It is a BCS Class 2 drug thus having low solubility. Thus, it's a good candidate for preparing a liquid solid tablet. Blonanserin was developed as an antipsychotic drug in Japan and approved for the treatment of schizophrenia. It belongs to a series of 4-phenyl-2-(1-piperazinyl) pyridines and acts as an antagonist at dopamine D_2, D_3, and serotonin 5-HT_{2A} receptors. Blonanserin has low affinity for 5-HT_{2C}, adrenergic α_1, histamine H_1, and muscarinic M_1 receptors, but displays relatively high affinity for 5-HT_6 receptors. In several short-term double-blind clinical trials, blonanserin had equal efficacy as haloperidol and risperidone for positive symptoms in patients with chronic schizophrenia and was also superior to haloperidol for improving negative symptoms. The Bioavailability **is** 55% due to low solubility. Blonanserin is rapidly absorbed from the gastrointestinal tract (except for the stomach) after oral administration and reaches a maximum plasma concentration (C_{max}) within 2 hours.

Binding to plasma proteins is almost 100% over the concentration range of 10 ng/mL-2 μg/mL with albumin contributing the most to binding. Blonanserin appears to be effective for a wide range of symptoms in adult patients with first episode and multiple episodes of schizophrenia.

Rational

- Blonanserin use to treat Schizophrenia and other bipolar disorder.
- It is BCS class II drug having low solubility.
- To increase dissolution rate of drug.
- It has short biological half-life of 4 hours.
- The affinity of Blonanserin for D_2 receptors is 20 and 94 fold higher than that of haloperidol and risperidone, respectively.
- Blonanserin has low affinity for 5-HT_{2C}, adrenergic α_1, histamine H_1, and muscarinic M_1 receptors which decrease certain adverse effects such as orthostatic hypotension, over sedation, weight gain, metabolic abnormalities, and peripheral anticholinergic side effects.
- To attenuate excipients in formulation, compare with other formulations like solid dispersions, and omit the method approaches like nanonisation, micronization techniques and soft gelatine capsule as its cost is low.
- These Liquid-solid systems formulate into immediate release or sustained unleash dose forms and gives constant dissolution rates (zero order release) to water insoluble medicine.

Objective

- To prepare Blonanserin liquisolid tablet to increase its aqueous solubility of oral administered dose.
- To Characterization and evaluation of prepared dosage form.
- To study the various formulations and process variables that effects on the drug release.
- Optimization and formulation using suitable experimental design.
- To study the kinetic models of drug.
- To perform stability study of the optimized formulation.
- Statistical treatment for the prepared dosage form.

Experimental work

Materials and equipment

Table 1. Name of chemicals

Chemical Names:	Role	Sources
Blonanserin	API	Zydus Research centre, Ahmadabad
PEG 600	Non volatile solvents	Balaji Chemicals, Ahmadabad
AVICEL PH200	Carrier	Balaji Chemicals, Ahmadabad
CAB-O-SIL	Coating material	Balaji Chemicals, Ahmadabad
SODIUM STARCH GLYCOLATE	Disintegrant	Balaji Chemicals, Ahmadabad

Table 2. Proposed Equipment to be used

Instrument	Manufacturer
U V spectrophotometer	Shimadzu UV 1800 Japan
Fourier Transform Infrared spectrophotometer	Shimadzu FTIR 8400S Japan
Analytical balance	Shimadzu AUX 220 Japan
Monsanto Hardness tester	Erection inst & engineering Ahmadabad
Dissolution apparatus	Electrolab TDL 08L Mumbai
Roche fabrilator	Electrolab Mumbai
Disintegrator	Electrolab ED 2L Mumbai

Water used was semi-quartz distilled. All other chemicals and reagents used were of analytical grade, procured commercially and used as such without further purification.

Preformulation Study

It is identified as the phase of experimental and formulation in which this can characterize appearance and chemical properties of API molecule in respect to develop safe, Stable and effective dosage form. This is the first step in the formulation of dosage form of a medicament. A main objective is to form the compatibility of the drug with excipients.

Following parameters are done in this
Physical State
Appearance and melting point

Characterization of blonanserin

State: Solid Powder
Color: Clear white colour
Odor: Odorless
Taste: Tasteless

Analytical method [60]

- **Determination of λ max for blonanserin**

For finding out the λ max of blonanserin, the drug is dissolved in 0.1 N HCl and allows mixing properly. The prepared (25 µg/ml) solution is scanned under UV spectro photometer between 200-400 nm wavelengths and the peak is measure.

- **Preparation of Standard calibration curve of blonanserin**

100 mg of Blonanserin is dissolved in 1.2 pH of 0.1N HCl, the makeup volume is done up to 100 ml in a 100 ml volumetric flask.

From the above solution 1 ml is taken and it is further diluted with same solvent and made up to 100 ml in another volumetric flask
From these stock solution 10 µg/ml amounts of 0.5, 1, 1.5, 2.0, 2.5, and 3 ml is withdrawn and the series is prepared
Absorbance is measure at 237 nm by UV/Vis double beam spectroscopy
Calibration curve is prepared using entire series from 5-30 µg/ml.

Drug excipients compatibility study

The compatibility study was carried out by using FTIR – 8400S (shimadzu corporation, Tokyo, Japan) for observing the purity of drug and compatibility of drug and excipients. The study was carried out by blending the powder sample with KBr pellets and pressed using disc. The disc was kept in between the spectro photo meter and spectrum is recorded.

Solubility Study[61]

This study was carried out by preparing the saturated solution of drug using different type of non aqueous solvent. This saturated solution is shaking in the shaker for specific time period under constant vibration. It is kept for 48 h at 25^0 C. After 48 hours, this solution was filtered and analyzed using UV spectro photo meter at 237 nm wave length.

Tablet preparation using Liquisolid techniques

- Selection of liquid vehicle
- Solubility of drug in a non-volatile vehicle is very important aspect in liquisolid systems. On the basis of the result of solubility test the PEG 600 was selected as a liquid vehicle. It contributes to the molecular dispersion in a non volatile solvent to improve dissolution rate.
- Loading Factor
- It is the ratio of amount of liquid medication to the amount of carrier material which is calculated by using LF = W/Q
- Where Liquid medication is mixture of drug and non volatile solvent and Avicel is a carrier material.
- It is used for the calculation of amount of carrier and coating matter in each batch.

Preparation method

- To prepare Liquisolid tablet first of all the drugs is mixed with the non volatile solvent properly which used as a liquid vehicle i.e. PEG 600
- The above solution is mixed with Avicel PH 200 which is used as a carrier material which gives flow ability to the liquid medication.
- The mixture is thoroughly blend in mortal for 20-25 minutes
- After this the coating material is used in this for coating of the powder mixture
- In the above mixture Sodium starch glycolate is used as a disintegrant
- The whole mixture is calculated using as per flow property of the powder measuring angle of repose in between 30 – 35^0
- Finally Talc and magnesium stearate were added as lubricant and glidant
- The tablet was compressed by using dry granulation method

Preliminary batch preparation

First of all the random powder quantity was selected and the preliminary batch was prepared by calculating the angle of repose

First batch was prepared by using the amount of avicel as a variable and amount of Cab o sil as a constant.

In another batch the amount of avicel is taken as constant and amount of cab o sil ii-s take as variable. Here the drug concentration is used 4 % w/w

Table 3. Composition Preliminary trials

Formulation	Drug (mg)	(%w/v)	W (mg)	Avicel PH 200 (mg)	Cab o sil (mg)	R=Q/q	Lf W/Q	SSG (mg)	Total Weight (mg)
Q1	4	2	217.5	200	13	19.230	0.29	50	397.06
Q2	4	2	217.5	225	17	16.176	0.2636	50	426.93
Q3	4	2	217.5	250	21	14.285	0.2416	50	456.80
Q4	4	4	145	275	25	12	0.4833	50	386.25
Q5	4	4	145	300	28	11.607	0.4461	50	415.09
Q6	4	4	145	325	31	11.290	0.4142	50	443.93
Q7	4	6	72.5	350	34	10.294	0.2071	50	447.02
Q8	4	6	72.5	375	37	10.135	0.1933	50	475.86
Q9	4	6	72.5	400	40	10	0.1812	50	504.74

Pre compression parameters

The flow ability of the powder is a vital for the performance of the tablet. Hence, the flow properties of the powder were measured before compression to tablets. The powder mixture of various formulations was evaluated by using angle of repose, bulk density, tapped density, compressibility index, and Hauser's ratio.

Bulk density

Accurately weighed 50 gm of blend; previously skilled 20 number sieves is transferred into 100 ml graduate. The powder was carefully equalized without compacting and therefore the unsettled apparent volume was noted.

Bulk density = Weight of the powder/Bulk volume of Powder

Tapped density

Accurately weighed 50 gm of the blend was transferred into 100 ml graduate. Initial volume was measured. The cylinder was tapped rapidly for 500 times from a distance of 14 + 2 mm and measured the tapped volume to the closest graduated units. The tapping was repeated for extra 750 times. Again the tapped volume was measured to the closest graduated unit. The tapped bulk density in gm/ml was calculated by using the subsequent formula.

Tapped density= Weight of powder taken/ Tapped Volume

Compressibility index

The propensity of the powder to be compressed is measured by compressibility and it also helps in measurement of settling property and inters particulate interaction.

Compressibility index (%) = $\rho t - \rho o * 100 / \rho t$

Where
ρt = Tapped density gram/ml, ρo = Bulk density gram/ml.

Hausner's ratio

The Hauser's ratio may be a number that's correlated to the flowability of a powder or granular material

Hausner's ratio= Tapped density/ Bulk density

Angle of repose

The angle of repose of blended powder was decided by funnel method. Accurately weighed powder blend was taken during a funnel. Height of the funnel was adjusted in such ways in which tip of the funnel just touches the apex of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose is calculated using the subsequent equation;

$\tan \theta = h/r$
Where, h and r are the peak and radius of the powder cone.

Tablet formulation

After weighing the calculated amount of drug and excipients, magnesium stearate and talc are added to the mixture blend as a lubricant and glidant respectively.
Tablet is prepared by using direct compression method

Post compression parameters

Thickness and hardness test

The thickness of the tablets decided using digital caliper; reading shown was noted. The hardness was measure by using Monsanto tester.

Hardness should be in between 4-7 Kg/cm^2

Friability test

The friability of the tablets decided using Roche friabilator. The percentage of friability was then calculated using the formula:

Friability $\%F = ([W - W]/W_O) * 100$

Where, Wo =initial weight of tablet; W = Final weight of tablet.
Friability should not more than 1%

Weight variation test

The test was performed as per USP by weighing 20 tablets individually on balance, calculating the typical weight, and comparing the individual tablet weights to the typical.
It should not be less than 90% and more than 110% of the average weight

In-vitro disintegration test

The test was administered on 6 tablets using tablet disintegration tester. Water at 37 ± 2˚C has been used as a disintegration media and therefore the time taken for complete disintegration of the tablet was noted with no passable mass remaining within the apparatus was measured.
Should not be more than 30 minutes

Wetting time

A bit of paper tissue was folded twice and placed in small Patrydish containing sufficient water. A tablet was kept on the paper and therefore the time for complete wetting of tablet was determined

Drug content determination

The average weight was calculated by selecting three random tablets. Tablets were powdered during a mortar and accurately weighed amount of tablet powder was taken from the blend and transferred it in to a 100 ml volumetric flask.10 ml of 0.1 N HCl was added and sonicated for 10 minutes. Then volume was mark up to 100 ml with 0.1 N HCl. The 1mL of final solution was diluted to 100mL with buffer (pH 1.2). The absorbance of above solution was measured in UV spectrophotometer at 237nm.

Dissolution studies

The dissolution test for tablets is that the same as that of conventional tablets. The discharge rate of Blonanserin from liquisolid tablets was studied using USP Dissolution apparatus II. The dissolution tests were done by using 900 ml of 0.1 N HCl pH 1.2, at 37 ± 0.5°C and 50 rpm. A sample (2 ml) of the solution was taken from the dissolution apparatus at 0, 5, 10, 15, 25, 35, 45 minutes intervals and diluted to 10 ml and replaced with 1ml of freshly dissolution medium. The samples were filtered. Absorbencies of those solutions were measured at 237nm using UV-Visible spectrophotometer.

Optimization of variable using full factorial design

A 3^2 full factorial design was accustomed statistically optimize the formulation parameters and evaluate main effects, interaction effects and quadratic effects of the preparation ingredients on disintegration time and in vitro release of formulations. The nonlinear computer-generated quadratic model is given as Eqn. ,

$$Y = b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2,$$

Where, Y is that the measured response concern to each factor level combination; b0 is an intercept; b1 to b22 are regression coefficients computed from the observed experimental values of Y, and X1 and X2 are the coded levels of independent variables. The terms X1X2 and Xi2 (i = 1, and 2) represent the interaction and quadratic terms, respectively. The dependent and independent variables selected are shown in Table 9 alongside their low, medium and high levels. Response analysis was evaluated by Design-Expert software.

The amount were selected supported a literature survey and preliminary trials. A design matrix comprising of 9 experimental runs was constructed as shown in Table.

Optimization data analysis and optimization model:

The aim of pharmaceutical formulation development is to develop a suitable formulation within the shortest period of your time using minimum trials. Really efficient thanks to enhance the worth of research and to attenuate the process development time is thru the planning of the experiment. So for optimization of liquisolid tablets of chlorpromazine, grid searches were conducted to seek out the composition of optimized formulations. Various 2D and 3D response surface graphs were provided by the Design-Expert software. By intensive grid search performed over the entire experimental region, an optimum formulation was selected which satisfies the desired criteria for liquisolid formulation.

Table 4. Coding variable

Code value	Actual value	
	X_1 (drug concentration (% w/v)* in polyethylene glycol (PEG) 600)	X_2 (Coating : carrier ratio)
-1	3	10
0	4	13
1	5	16

Dependent variable Y_1 and Y_2 are constraint that is drug release in 30 minutes and time of disintegration respectively

Table 5. 3^2 Full factorial design matrix with interaction terms batches

Formulation	X_1	X_2	X_1 (%w/v)	X_2 R=Q/q
R1	-1	-1	3	10
R2	0	-1	4	10
R3	1	-1	5	10
R4	-1	0	3	13
R5	0	0	4	13
R6	1	0	5	13
R7	-1	1	3	16
R8	0	1	4	16
R9	1	1	5	16

Table 6. Drug concentration in PEG

Drug (mg)	Conc. (%w/v)	PEG (ml)	PEG (mg)	Weight of liquid medication (mg)
4	3	0.13	145.6	149.6
4	4	0.10	112	116
4	5	0.08	89.6	93.6

Kinetic Model of release data

Values obtained from in-vitro diffusion studies were fitted to varied kinetic equations. The kinetic models used are

Zero order equations (Q=k0t),

Drug dissolution as the formulation do not differentiate and release medicament slowly (assuming as the area of contacting may not change and no equilibrium conditioned are obtained)

The equation for zero order drug diffusion plots is: Ct = C0 – Kt

Where, Ct = concentration remaining at time t,
Co = original concentration,
t = time,
K = diffusion rate
A plot of preference shares drug diffusion versus time would be linear if the drug diffusion follows zero order (i.e. Concentration independent diffusion).

First order equation

The use of this modet to API dissolution study as it was first prepared by Gibaldi and Fieldmen (1967) and afterwards by Wagner (1969). This model is very usefuk to describe the absorption and excreation of some medicament. As also it is very hard to conceptualize these mechanisms in a writable basis

Table 7. Composition of factorial batch

Formulation	Drug (mg)	X_1 (%w/v)	W (mg)	Avicel PH 200 (mg)	Cab o sil (mg)	X_2 R=Q/q	Lf W/Q	SSG (mg)	Total Weight (mg)
R1	4	3	149.6	180	18	10	0.8311	50	140
R2	4	4	116	220	22	10	0.5272	50	153
R3	4	5	93.6	260	26	10	0.36	50	166
R4	4	3	149.6	234	18	13	0.6393	50	205
R5	4	4	116	286	22	13	0.4055	50	228
R6	4	5	93.6	338	26	13	0.2769	50	251
R7	4	3	149.6	288	18	16	0.5194	50	270
R8	4	4	116	352	22	16	0.3295	50	303
R9	4	5	93.6	416	26	16	0.225	50	336

The equation for first order diffusion plot is

Log C = $\frac{logC0Kt}{2.303}$

A plot of log percentage of remaining drug versus time would be linear, if the drug diffusion follows first order (i.e. Concentration dependent diffusion)

Higuchi equation

As a scientist Higuchi promote several theoretical theories to learn the release of water soluble and less soluble APIs incorporated in Semi solid and solid matrixes. In a common ways it can be possible to obtain the Higuchi model to the following calculation

$Q=kt^{1/2}$

Higuchi drug release as compared to the diffusion process with the basis ofFick's law, square root time dependent

Hixson and crowell model

It has been recognizing as the particular area which is proportional to the cubic root of its volume which can be derived as an equation which relate as the below

$\sqrt[3]{W_0} - \sqrt[3]{W_t} = K_s t$

Where W_0 is the initial weight of API in the formulation, W_t remaining weight of API

This expression is use toward the pharmaceutical dosage form in which the dissolution is parallel to the surface of medicament proportionally in case that its earlier geometrical forms keep uniforms all the time.

Korsmeyer and Peppas equation

It was developed as an easy, semi empirical model, which was corresponding to the release of the drug from time intervals.

$[1 - M_t / M]^{1/3} = 1\text{-}k_t$

Where, Mt = mass of drug diffusion at time t,
M = mass diffusion at the infinite time,
K = rate of abrasion,
t = time

Thus a plot of $[1 - Mt / M]^{1/3}$ vs. the time might be going to be linear. If the diffusion of medicament from the surface is erosion controlled.

In this model, drug within the outside layer exposed to the washing solution is dissolved first then diffuses out of the matrix. This process continues with the interface between the bathing solution and therefore the solid drug moving towards the inside. Obviously, for this system to be diffusion controlled, the speed of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Table 8. Determination of dissolution release mechanism

Release exponent (n)	Drug transport mechanism	Rate as the function of time
0.5	Fickian diffusion	$t^{0.5}$
$0.5 \leq n \leq 1.0$	Anomalous transport	t^{n-1}
1.0	Case II transport	Zero order release
≥ 1.0	Super Case II Transport	t^{n-1}

Table 9. Graph plot for kinetics model fitting

Kinetic Model	X - Axis	Y - Axis
Zero Order	% drug release	Time
First Order	Log % drug release	Time
Higuchi Model	% drug unreleased	$Time^{1/2}$
Hixson Crowell	% drug unreleased	$Time^{1/3}$
Korsmeyer and peppas	Log % drug release	Log time

RESULTS AND DISCUSSION

Calibration curve of blonanserin

The calibration curve was measured at 237 nm for blonanserin concentration range 5–30 µg/ml series. The data of this curve is given in table 6.1. The observed r^2 is 0.9982.

Table 8. Standard Values of Blonanserin at 237 nm

SR. NO	Conc. (µg/ml)	Abs (N=3)
1	0	0
2	5	0.158
3	10	0.318
4	15	0.446
5	20	0.612
6	25	0.745
7	30	0.856

Compatibility Study

The compatibility study of pure drug and its excipients were carried out in FTIR spectroscopy in which it's determined that all the peaks of pure blonanserin spectra are also seen in the physical mixture so that they are compatible with each other.

Table 9. Drug-Excipients compatibility studies by FT-IR

Sr. No.	Assignment	Peak report in Pure Drug (cm-1)	Peak report in Physical Mixture (cm-1)
1	N -H stretch	3413.20	3417.62
2	C-H (alkane stretching)	2927.92	2906.24
3	C-N stretch	1626.29	1633.36

Solubility Study

Different types of non volatile solvent were used to determine the solubility of blonanserin. Due to the solubility of the drug in non volatile solvent, Dissolution improves by molecular dispersion. The results are shown in table 6.3 and on the basis of this results PEG 600 was selected as a liquid solvent.

Table 10. Blonanserin solubility

Solvent	Solubility (mg/ml)
Glycerine	0.18
PEG 400	3.45
PEG 600	3.74
Propylene Glycol	2.15
Tween 80	2.90
Tween 20	2.34
Span 80	2.14
Span 20	1.94

Evaluation of Preliminary batch of blonanserin Liquisolid tablet

Pre compression parameters of Preliminary batch

Table 11. Pre compression parameters of Preliminary batch

Formulation	BD (gm/ml)	TD (gm/ml)	C.I. (%)	H.R.	(θ)
Q1	0.52 ± 0.03	0.75 ± 0.07	14.0 ± 0.3	1.132±0.02	26.15^0
Q2	0.58 ± 0.02	0.71 ± 0.05	13.3 ± 0.3	1.23±0.02	29.29^0
Q3	0.53 ± 0.05	0.66 ± 0.08	18.9 ± 0.7	1.21±0.04	30.43^0
Q4	0.53 ± 0.07	0.615 ± 0.07	14.2 ± 0.5	1.20±0.03	28.44^0
Q5	0.51 ± 0.05	0.65 ± 0.06	14.3 ± 0.6	1.37±0.05	33.86^0
Q6	0.53 ± 0.04	0.65 ± 0.05	17.1 ± 0.8	1.14±0.03	36.49^0
Q7	0.55 ± 0.03	0.630 ± 0.04	15.5 ± 0.4	1.27±0.04	34.12^0
Q8	0.52 ± 0.02	0.66 ± 0.06	13.1 ± 0.3	1.26±0.02	31.51^0
Q9	0.55 ± 0.03	0.67 ± 0.07	15.9 ± 0.3	1.38±0.02	30.77^0

Post compression parameters of Preliminary batch

Table 12.Post compression parameters I

Formula-tions	Weight variation (mg)	Thickness (mm)	Friability %	Broken tablet
Q1	396.0±0.65	3.08±0.02	0.56	None
Q2	416.6±0.95	3.14±0.16	0.74	None
Q3	462.8±0.05	3.22±0.28	0.65	None
Q4	392.66±0.25	3.18±0.08	0.41	None
Q5	417.09±0.25	3.15±0.10	0.45	None
Q6	442.7±0.16	3.00±0.12	0.48	None
Q7	443.6 ±0.02	3.08±0.05	0.56	None
Q8	478.66±0.15	3.12±0.07	0.45	None
Q9	506.7±0.14	3.18±0.02	0.58	None

Table 13. Post compression parameters II

Formula-tions	Hardness (kg/cm3)	Wetting Time (Seconds) (n=3)	Disintegration Time (Seconds) (n=3)	Drug content (%)
Q1	3.45±0.36	43 ± 12	38 ± 15	93.31±0.61
Q2	3.67±0.32	33 ± 15	34 ± 13	94.63±0.62
Q3	3.42±0.25	46 ± 2	29 ± 10	97.37±0.62
Q4	3.75±0.14	29 ± 5	34 ± 6	99.67±0.10
Q5	3.86±0.12	32 ± 2	37 ± 6	98.06±
Q6	3.94±0.20	38 ± 6	522 ± 8	94.88±0.46
Q7	3.97±0.35	51 ± 10	43 ± 5	92.3±0.68
Q8	3.76±0.30	56 ± 6	48 ± 12	84.8±0.05
Q9	3.8±0.4	53±3	36±3	93.6±0.06

In vitro drug release

Table 14. In vitro drug release of Preliminary batch

Formulation	% Drug release in minutes									
	0	5	10	15	20	25	30	40	50	60
Q1	0	19.5	26.8	37.1	46.9	58.8	67.6	76.6	86.6	92.6
Q2	0	22.4	31.5	42.1	49.8	61.8	72.9	86.1	92.8	95.4
Q3	0	24.26	31.02	42.15	49.45	66.69	71.53	81.20	88.22	92.87
Q4	0	33.2	48.0	65.2	74.8	86.8	95.6	99.2	-	-
Q5	0	31.6	40.4	54.9	64.4	86.9	93.2	97.4	99.5	-
Q6	0	29.9	37.6	49.6	56.7	69.4	76.3	85.6-	94.8	96.7
Q7	0	27.75	36.79	43.16	58.21	62.43	70.87	76.13	79.31	84.07
Q8	0	25.68	34.89	40.94	55.21	59.2	67.26	72.24	75.23	82.68
Q9	0	19.97	27.13	31.83	42.84	46.56	52.26	58.44	67.54	76.97

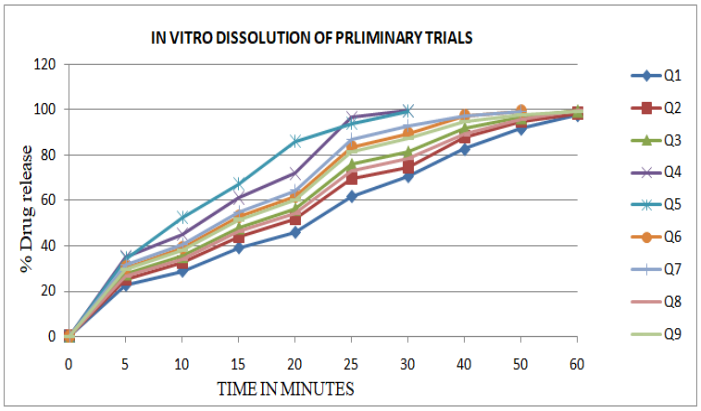


Fig. 1. In vitro dissolution of Preliminary batch

Discussion on preliminary trials

In this primary trials different types of carrier and coating material ratio (i.e. R = Q/q) taken for preparation of blonanserin liquisolid tablet. The given results data show that when R value is in between 10 to 18 it gives optimum level of dissolution rate.

This optimize batch having the concentration of 4% w/v and having better dissolution rate of than other batch.

By this information the factorial batch was selected using the two variables (i.e. Value of R and Drug concentration) having R value between 10 to 16 and drug concentration of 4±1 % w/v.

Evaluation of Factorial batch of blonanserin Liquisolid tablet

Pre compression parameters of Factorial batch

Table 15. Pre compression parameters of Factorial batch

Formulation	BD (gm/ml)	TD (gm/ml)	C.I. (%)	H.R.	(θ)
R1	0.2±0.03	0.26±0.03	23.07±0.2	1.3±0.023	28.8±1.23
R2	0.2±0.04	0.25±0.03	20±0.5	1.25±0.035	33.69±1.42
R3	0.33±0.03	0.39±0.01	15.38±0.4	1.18±0.026	31.21±3.22
R4	0.32±0.02	0.37±0.04	13.5±0.6	1.15±0.034	30.40±2.54
R5	0.25±0.14	0.29±0.05	13.79±0.03	1.16±0.024	29.7±1.68
R6	0.33±0.17	0.38±0.45	13.15±0.25	1.15±0.036	29.7±3.8
R7	0.32±0.24	0.42±0.65	23.12±0.16	1.31±0.03	29.04±2.3
R8	0.37±0.16	0.43±0.25	13.95±0.35	1.16±0.01	29.04±1.0
R9	0.33±0.26	0.38±0.45	13.15±0.17	1.15±0.024	30.40±3.6

Post compression parameters of Factorial batch

Table 16. Post compression parameters I

Formula-tions	Weight variation (mg)	Thickness (mm)	Friability %	Broken tablet
R1	146.12±2.1	3.08±0.02	0.56	None
R2	158.02±3.6	3.14±0.16	0.74	None
R3	167.93±3.4	3.22±0.28	0.65	None
R4	205.12±1.6	3.18±0.08	0.41	None
R5	226.02±3.4	3.15±0.10	0.45	None
R6	254.93±3.6	3.00±0.12	0.48	None
R7	275.12±4.2	3.08±0.05	0.56	None
R8	329.02±1.6	3.12±0.07	0.45	None
R9	337.93±3.8	3.18±0.02	0.58	None

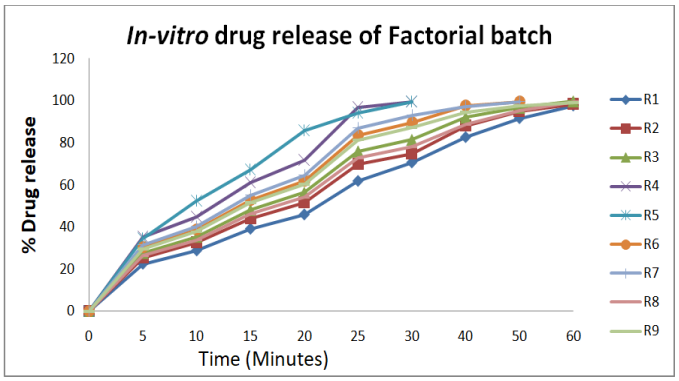
Table 17. Post compression parameters II

Formula-tions	Hardness (kg/cm3)	Wetting Time (Seconds) (n=3)	Disintegration Time (Seconds) (n=3)	Drug content (%)
R1	4.60±0.2	30±6	28±3	97.31±0.61
R2	5.2±0.4	36±6	36±4	94.63±0.62
R3	4.8±0.2	48±5	39±3	93.37±0.62
R4	4.6±0.3	52±4	27±4	97.67±0.10
R5	4.8±0.1	46±4	37±5	96.33±0.68
R6	4.4±0.6	58±6	42±4	92.88±0.46
R7	5.4±0.3	47±3	52±3	98.06±0.30
R8	4.6±0.2	42±2	47±4	95.13±0.05
R9	5.2±0.4	49±3	36±3	94.8±0.06

In vitro drug release

Table 18. In vitro drug release of Factorial batch

Formulation	% Drug release in minutes									
	0	5	10	15	20	25	30	40	50	60
R1	0	22.5	28.8	39.1	45.9	61.8	70.6	82.6	91.6	97.6
R2	0	25.4	32.5	44.1	51.8	69.8	74.9	88.1	94.8	98.4
R3	0	27.6	35.3	48	56.3	75.9	81.4	92	96.7	99.7
R4	0	35.2	45	61.2	71.8	96.8	99.6			
R5	0	34.4	52.4	67.3	86	94.1	99.5			
R6	0	30.4	38.9	52.8	62	83.6	89.6	97.6	99.5	
R7	0	31.6	40.4	54.9	64.4	86.9	93.2	97.4	99.5	
R8	0	26.6	34	46.2	54.2	73.1	78.4	89	95.6	99.6
R9	0	29.6	37.8	51.5	60.3	81.4	87.3	94.6	97.6	99.1



Fig, 2. In vitro dissolution

Discussion of Factorial batches

Following are the outcome of the factorial batch

Pre compression parameters

The angle of repose value was found in range of 28^0 to 34^0. Bulk and tapped density were in range of 0.2 to 0.33 and 0.26 to 043 respectively. The Carr's index and Hauser's ratio was in between 13 – 23 and 1.11 to 1.31 respectively. Thus, over all the powder contain fair flow ability which can be easily directly compressed.

Post compression parameters

The tablet show hardness in between 4 – 7 Kg/cm^3 and it shows less weight variation. The friability was less than 1% which show tablets has less mechanical resistance as indicated in IP. The in vitro disintegration time was less than 1 mins which shows tablet can easily be disintegrated in the stomach.

In vitro dissolution study data was carried out in 0.1 N HCl by using USP dissolution apparatus 2 were shown in table 6.11 and the comparison plot was shown in fig 11 by help of Ms Excel. The formulation R4 and R5 shows the maximum Dissolution rate than other. More than 95% were dissolute in less than 30 minutes of time. From the other batches R1 and R2 shows less dissolution rate. From this result it exhibit that the concentration and ratio of carrier materials are very important to optimize the dissolution rate.

Comparison of conventional tablet (marketed product) and liquisolid table (R4 batch)

The in vitro dissolution of Conventional tablet blonitas (4 mg blonanserin) used to study this comparison which was purchase by market. The in vitro dissolution data of both the tablet were shown in table 6.12

Table 19. In vitro drug release comparison

Time (Minutes)	% drug release in time		
	API	Marketed product	R4
0	0	0	0
5	23.55	29.02	35.2
10	28.66	35.32	45
15	31.84	39.33	61.2
20	36.93	45.5	71.8
25	39.28	48.41	96.8
30	42.69	52.61	99.6
40	44.8	55.32	
50	47.33	58.415	
60	52.76	65.25	
90	58.92	72.5.96	

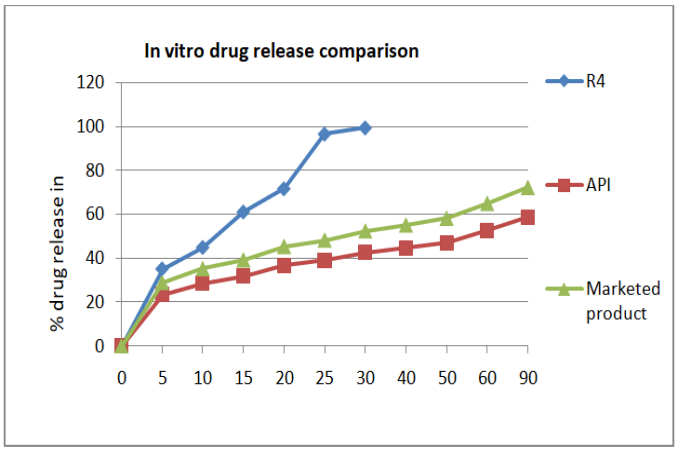


Fig. 3. In vitro dissolution comparison

Release kinetics modeling of in vitro dissolution data

Table 20. Release kinetics modeling of in vitro dissolution data

	R1	R2	R3	R4	R5	R6	R7	R8	R9
Zero order									
R^2	0.93706	0.9944	0.94659	0.95753	0.9300	0.9868	0.9823	0.9452	0.9207
B	0.01149	1.4115	1.3847	1.3961	1.6405	2.7885	2.6817	1.6749	1.3301
A	1.40484	24.427	28.8660	26.7467	31.050	19.466	25.353	28.473	33.335
First order									
R^2	0.95129	0.9207	0.90312	0.91278	0.9006	0.9850	0.9547	0.9133	0.8808
B	0.02508	0.0107	0.00986	0.01047	0.0112	0.0190	0.0181	0.0116	0.0092
A	0.41848	1.4694	1.51588	1.49459	1.5453	1.4718	1.5140	1.5223	1.5562
Higuchi									
R^2	0.99036	0.9972	0.99773	0.98957	0.9836	0.9868	0.9942	0.9727	0.9624
B	15.00779	14.743	14.6080	14.6454	16.077	21.477	21.118	16.304	14.199
A	-15.584	-9.886	-5.5287	-7.5163	-4.5618	-18.433	-12.968	-7.3660	-0.5488
Hixson crowel									
R^2	-0.97808	-0.9664	-0.9466	-0.9577	-0.9300	-0.9868	-0.9823	-0.9452	-0.9207
B	-0.48401	-0.4710	-0.4615	-0.4653	-0.5463	-0.9292	-0.8939	-0.5583	-0.4433
A	27.03110	25.190	23.7113	24.4177	22.983	26.844	24.882	23.842	22.221
Korsmeyer and peppas									
R^2	0.98914	0.9878	0.98377	0.98638	0.9772	0.9809	0.9965	0.9814	0.9765
N	0.64715	0.6016	0.57350	0.58506	0.5628	0.6151	0.6156	0.5788	0.5446
A	-1.1418	-1.043	-0.9773	-1.0061	-0.9096	-0.9184	-0.8918	-0.9428	-0.9169

B=Slope
a= Intercept
r^2=Square of correlation intercept
N = Diffusion exponent

Discussion on the basis of kinetics model

The kinetics of in vitro release of blonanserin liquisolid tablet is given in table 20 They were fitted in Higuchi, zero order, first order, Korsmeyer and peppas and Hixson Crowell equation to identify the release mechanism of tablet by in vitro dissolution. The co efficient of regression equation R^2 was well fitted in zero order and Higuchi equation which shows that the drug release was dependent to the concentration of the drug and diffusion of drug occurs. Apart from this, from the Korsmeyer and peppas plot it was assumed that the non-fickian diffusion occurs as the exponent n value was in between 0.5 to 1.0.

Stability study

Table 21. parameter of batch R4 after accelerated stability study

Parameter	At 0 time	After 1 month
% Drug Content	97.67	96.46
Weight uniformity	205.12	203.15
Hardness	4.6	4.6
Disintegration time	27	27

Table 22. *In vitro* dissolution data of batch R4

Time	% CPR at time 0 (%)	CPR after 1 month (%)
0	0	0
5	35.2	34.9
10	45	44.8
15	61.2	62.6
20	71.8	71.6
25	96.8	96.4
30	99.6	99.4

To study accelerated stability study the tablet was kept for one month at 40^0 C ± 2^0 C in a humidity jar at 75% ± 5% RH. Sample shows no change in their post compression evaluation and *in vitro* dissolution**.**

Summary and conclusion

In this present research, a blonanserin liquisolid tablet was prepared by using Cab o sil and avicel coating and carrier materials respectively. PEG 600 was used as a non volatile solvent because blonanserin has highest solubility in it.

Compatibility study between drug and excipients were done through FTIR and calibration was finding through UV Spectroscopy.

Comparison of dissolution rate was done between R4 and marketed product which shows it take less than half time to completely dissolve than marketed product.

From this, we have concluded following things,

- The solubility study of Blonanserin in presence of PEG 600 was high in comparison with propylene glycols, Tweens & spans.
- The liquisolid technique was found to be a promising approach for improving the dissolution of poorly soluble drugs like Blonanserin.
- The Dissolution of Blonanserin was significantly increased in liquisolid formulation compared to the marketed product.
- The IR spectra indicate there was no interaction between the drug and excipients. The increased dissolution rate could also be thanks to increased wetting and increased area of the particles.
- Drug content & In Vitro dissolution studies of blonanserin liquisolid compacts it had been concluded that the formulation R4 is that the best formulation.
- It also shows that the drug posses non fickian diffusion through in vitro dissolution which was studied from kinetics model theory.

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