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Enhancement of solubility of ambrisentan by using solid dispersion techinique

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Abstract
The present work was aimed to enhancement of solubility of Ambrisentan by using solid dispersion technique by solvent evaporation technique. Ambrisentan is a class II drug and hence it is formulated by using solid dispersion technique to increase solubility of drug with the aid of β-cyclodextrin. Solid dispersion was prepared by combining of drug and carrier. The physical mixtures were prepared by solvent evaporation technique accordingly with the composition given in table. The ingredients like drug and carrier were accurately weighed (in different ratios 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7) and mixed in porcelain dish with a stirrer for 10 min to get uniform mix by using ethanol. The above substance was dried. These are sieved to obtain granules by using sieve no.20. The blended powder was filled into capsules. The observed results reveals that carrier have significant effect on drug release up to 1 hr after successful development of solid dispersion containing Ambrisentan and β-cyclodextrin carrier in different ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7).

Keywords: ambrisentan, β-cyclodextrin, ethanol

Introduction
In pharmaceutical companies major work is going on in the field of drug discovery, in the anticipation of finding new therapeutic approaches and improving drugs for existing therapeutic areas. Among the five key physicochemical properties in the early compound screening including pka, solubility, permeability, stability and lipophilicity, poor solubility tops the list of undesirable compound properties. Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other properties of compound and add undesirable properties [1] can influence both pharmacokinetic and pharmacodynamic properties of the compound and finally may affect the bioavailability of the compound. Therefore, there is need of a new approach for enhancing solubility of drug.

Solid dispersions [2]
The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophilic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemical (e.g. rate of absorption) constraints. The solid dispersion components consist mainly of active pharmaceutical ingredients (API), the polymer, plasticizers, stabilizers, and other agents.

Advantages of solid dispersion [3]
The major advantages of solid dispersions is that it improves the dissolvability of a poorly water soluble drug in a pharmaceutical composition and results in rapid dissolution rates thereby improving the bioavailability of drug.

Rapid disintegration of oral tablets
Drug is formulated with hydrophilic carrier (eg PEG) as a solid dispersion to increase its aqueous solubility and dissolution .Then super disintegrant (eg croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self -medication even without the aid of water.

As a formulation vehicle
Solid dispersions can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain.

Particles with reduced particle size
Solid dispersions represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers, thus a high surface area is formed, resulting in an increased dissolution rate and consequently improved bio availability.

Particles with improved wettability
Enhancement of drug solubility is released to the drug wettability. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts when used, significantly increase the wettability of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore results in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release rate.

Drugs in amorphous state

The enhancement of drug release can usually be achieved if the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that if drugs precipitate it is as a met stable polymorphic form with higher solubility than the most stable crystal form.

Disadvantages of solid dispersion [4]

Disadvantages of solid dispersions are mainly related to their instability. Basically changes occur in several systems in crystallinity and a decrease in dissolution rate with ageing and system may be destabilized through physical treatment such as pulverization and ageing. There is more deteriorating effect f moisture and temperatures on solid dispersions that on physical mixture.

Usually solid dispersions are prepared with water soluble low melting point synthetic polymers such as polyvinyl pyrrolidone, mannitol or polyethylene glycol. These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/polymer) ratio.

An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of carrier, i.e.; more than 50% to 80% w/w, is required to achieve the desired dissolution.

Solid dispersion is a high energy metastable form. Phase separation, crystal growth or conversion from the amorphous to the crystalline form during storage decrease solubility and dissolution rate and results in variable oral bioavailability.

Methods of preparation of solid dispersions

Various methods have been developed for preparation of solid dispersions, these methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete), and formation of different phases is observed. Phase separation like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted.

1. Solvent evaporation method
2. Modified solvent evaporation method
3. Melting /fusion method
4. Solvent- melting method
5. Kneading method
6. Co-grinding method
7. Co-precipitation method
8. Spray drying method
9. Gel entrapment technique
10. Direct capsule filling
11. Lyophilization technique

The brief description of the methods is as follows:

Solvent evaporation method

After complete dissolution of drug and carrier in organic solvent, the solvent is evaporated. The solid mass is ground, sieved and dried. Prepared solid dispersions of ofloxacin with polyethylene glycol by solvent evaporation method [5].

Materials and Methods

Ambrisentan is an orally active selective type A endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension. It is approved in Europe, Canada and the United States for use as a single agent to improve exercise ability and delay clinical worsening. In addition, it is approved in the United States for use in combination with tadalafil to reduce the risks of disease progression, hospitalization and to improve exercise ability. Studies establishing the efficacy of Ambrisentan included patients with both idiopathic and heritable pulmonary arterial hypertension and those with pulmonary arterial hypertension associated with connective tissue diseases.

Synonyms

(2S)-2-[(4, 6-dimethylpyrimidin-2-yl) oxy]-3-methoxy- 3, 3-diphenylpropanoic acid

Chemical formula

$C_{22}H_{22}N_2O_4$

Molecular weight

378.4

Structure

Structure of Ambrisentan is as shown in the Figure 1

Ambrisentan is a classII drug and hence it is poorly soluble drug and which has longer half life (15 hours) hence it is formulated by using solid dispesion technique to increase solubility of the drug by using β-Cyclodextrin. List of chemicals used in study and their manufacturers is shown in Table 1 and List of equipments used in study and their manufacturers is shown in Table 2.

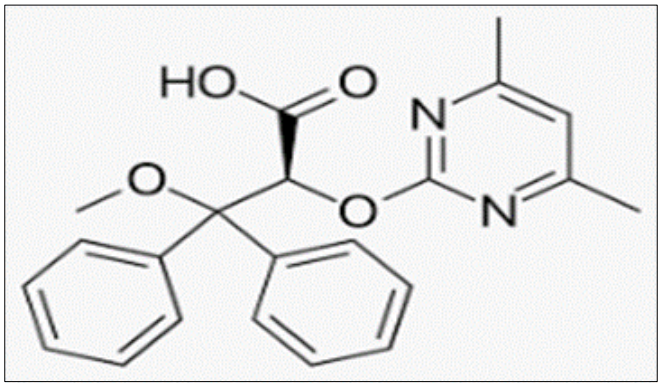

Fig 1: Structure of ambrisentan

Table 1: List of chemicals used in study and their manufacturers

S. No	Chemicals	Manufacturer	Purpose
1.	Ambrisentan IP	MSN Laboratories Limited Formulation Division	API
2.	β-Cyclodextrin	Yarrow chem products	Carrier
3.	Ethanol	Delta	Solvent
4.	Distilled water	Institutional supply	Solvent

Table 2: List of equipments used in study and their manufacturers

S. no	Equipment	Manufacturer
1	Electronic balance	Infra instrument pvt. Ltd-Chennai
2	Dissolution apparatus USP2	Labindia
3	UV spectrophotometer	Shimadzu UV-1800 Double beam spectrophotometer
4	Hot air oven	Darvin

Preformulation studies [6, 7]

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable, efficacious and safe dosage form. Hence Preformulation studies were carried out on the obtained samples of drug for identification and compatibility studies.

Identification test

The obtained sample was examined by infrared absorption spectral analysis and was compared with the reference standard IR spectrum of Ambrisentan.

Solubility

Solubility is determined by taking small amount of sample in a test tube and solvent is added based upon dispersion of solid weather it is Freely Soluble, sparingly soluble, very slightly soluble.

Compatibility Studies

The compatibility of drug and carrier under experimental condition is important prerequisite before formulation. Incompatibility between drug and excipients can alter stability and bioavailability of drug, thereby, affecting its safety and efficacy. Study of drug–excipients compatibility is an important process in the development of a stable solid dosage form. Drug–excipients compatibility testing at an early stage Ambrisentan IP in the selection of carrier that increases the solubility of the drug.

Fourier transform infrared spectroscopy (FTIR) studies

The drug- polymer and polymer-polymer interaction was studied by FTIR. Two percent (w/w) of the sample with respect to a potassium bromide disc was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm–1 using cosine apodization. The characteristic peaks were recorded. Ratio of Drug and Excipients taken for compatibility studies is shown in Table 3.

Table 3: Ratio of Drug and Excipients taken for compatibility studies

Ingredients	Ratio of drug and excipients
Ambrisentan	1:0
Ambrisentan + carrier (β-Cyclodextrin)	1:1

Estimation of Ambrisentan

Determination of λmax of ambrisentan in 7.4 P^H phosphate buffer

Stock solution

Standard stock solution was prepared by dissolving 100 mg drug in few drops of ethanol to it add 100ml of 7.4 P^H Phosphate buffer to get concentration of 1000 µg/ml. From this 1ml is taken in 10ml standard flask make up volume with 7.4 P^H Phosphate buffer to get concentration of 100µg/ml.

Method development

Aliquots of stock solution was further diluted with 7.4 P^H Phosphate buffer to get working solution of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4.0, 4.5, 5.0µg/ml and the working standards were scanned between 200 - 400 nm which shows maximum absorbance at 264 nm. The same absorbance was used for the development of calibration curve.

Preparation of drug and carrier complex by using solvent evaporation method [28, 29]

Physical mixture 1

In china dish accurate weight of Ambrisentan was taken to this add few ml alcohol. From this Specified amount of Ambrisentan is taken for dissolution study.

Physical mixture 2

In china dish the drug Ambrisentan and complexing agent β-cyclodextrin are taken in the proportion of 1:1. To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Physical mixture 3

In china dish the drug Ambrisentan and complexing agent β-cyclodextrin are taken in the proportion of 1:2. To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Physical mixture 4

In china dish the drug Ambrisentan and complexing agent β-cyclodextrin are taken in the proportion of 1:3. To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Physical mixture 5

In china dish the drug Ambrisentan and complexing agent β-cyclodextrin are taken in the proportion of 1:4. To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Physical mixture 6

In china dish the drug Ambrisentan and complexing agent β-cyclodextrin are taken in the proportion of 1:5. To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Physical mixture 7

In china dish the drug Ambrisentan and complexing agent β-cyclodextrin are taken in the proportion of 1:6. To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Physical mixture 8

In china dish the drug Ambrisentan and complexing agent β-cyclodextrin are taken in the proportion of 1:7. To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Design

P1, P2, P3, P4, P5, P6, P7 and F8 were designed to optimize the concentration of β-cyclodextrin and to study the effect of β-cyclodextrin.

The prepared dispersions are taken from each formulation. These formulations are passed through sieve No 20 to obtain granules. From these physical mixtures drug quantity equivalent to 5mg is weighed. These are filled into the capsules and those solid dispersions are evaluated.

Optimization of formulation ingredients in preparation is shown in Table 4.

Table 4: Optimization of formulation ingredients in preparation

S. No	Physical mixtures	Drug	Carrier	Composition	Solvent (ethanol)
1.	P1	100mg	-------	-------	-------
2.	P2	1000mg	β-cyclodextrin	1: 1	5-10ml
3.	P3	1000mg	β-cyclodextrin	1: 2	5-10ml
4.	P4	1000mg	β-cyclodextrin	1: 3	5-10ml
5.	P5	1000mg	β-cyclodextrin	1: 4	5-10ml
6.	P6	1000mg	β-cyclodextrin	1: 5	5-10ml
7.	P7	1000mg	β-cyclodextrin	1: 6	5-10ml
8.	P8	1000mg	β-cyclodextrin	1: 7	5-10ml

Evaluation parameters [8, 9]

***In-vitro* dissolution studies of solid dispersions**

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP II paddle method and 900ml of distilled water as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Solid dispersion was placed in the vessel and the vessel was covered the apparatus was operated for 1 hr in distilled water at 50 rpm. At definite time intervals of every 10 min a 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 254nm using UV-spectrophotometer.

Release kinetics

The analysis of drug release mechanism from a physical mixture form is an important but complicated process and is practically evident in the case of dispersion systems. As a model-dependent approach, the dissolution data was fitted to popular release models such as zero-order, first-order equations, which have been described in the literature. The order of drug release from dispersions was described by using zero order kinetics (or) first order kinetics.

Results and Discussion

Solubility

Ambrisentan is a white to off-white crystalline substance that is practically insoluble in water (0.06 mg/ml), but soluble in alkaline buffer solutions and a range of organic solvents.

Drug excipient compatibility studies

FTIR spectra of pure drug

FTIR spectra of pure drug are shown in Figure 2 and Interpretation of pure drug functional groups and characteristic absorption is shown in Table 5.

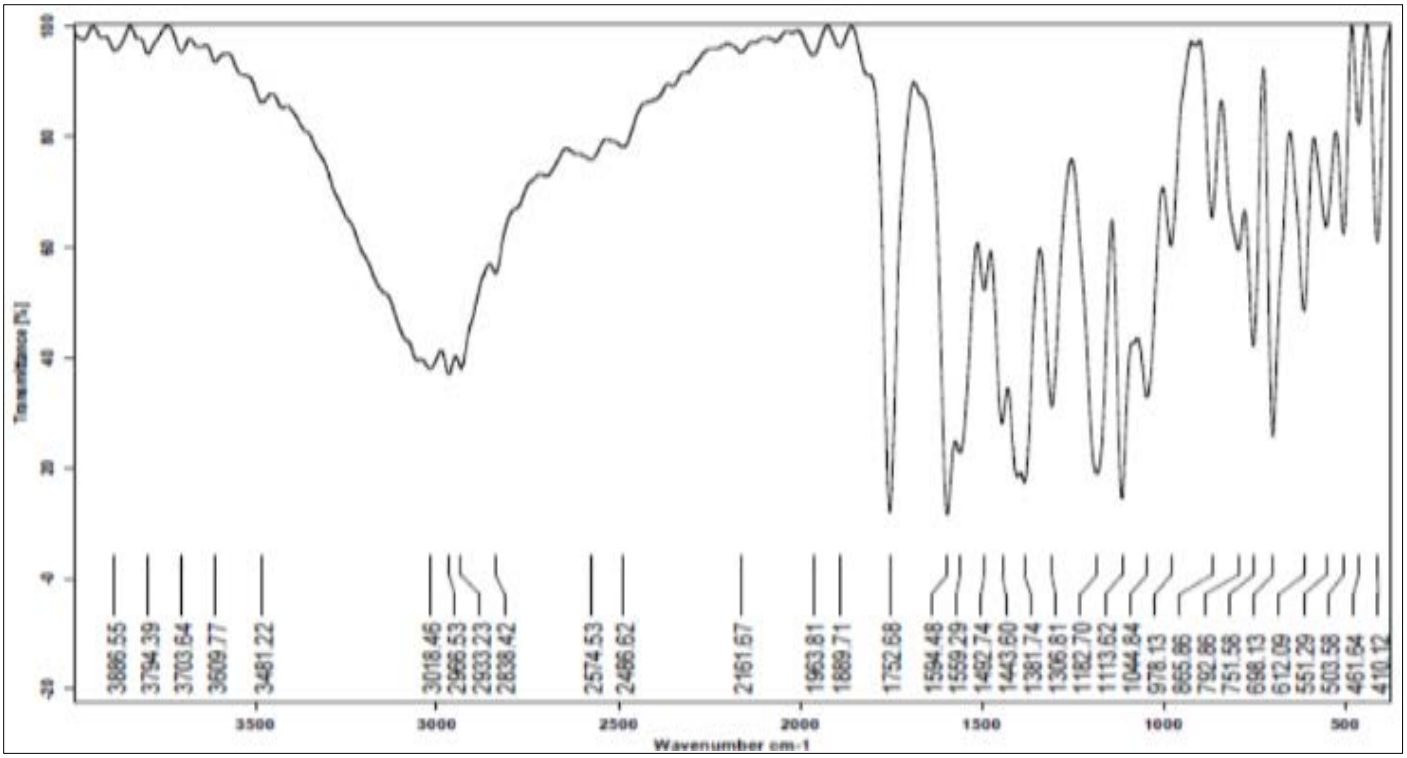

Fig 2: FTIR spectra of pure drug

Table 5: Interpretation of pure drug functional groups and characteristic absorption

S. No	Functional group	Characteristic absorption wave number (cm^{-1})
1.	- C=O (Acid group)	1752.68
2.	- CH_3 (Methyl group)	1381.74
3.	- C=N(Pyrimidine structure)	1492.74
4.	-C - O - C-	1182.70
5.	-O-H	3481.22

FTIR spectra of drug and β-cycloderxtrin: FTIR spectra of Drug and β- Cycloderxtrin are shown in Figure 3 and Interpretation of pure drug and β-cyclodextrin functional groups and characteristic absorption is shown in Table 6.

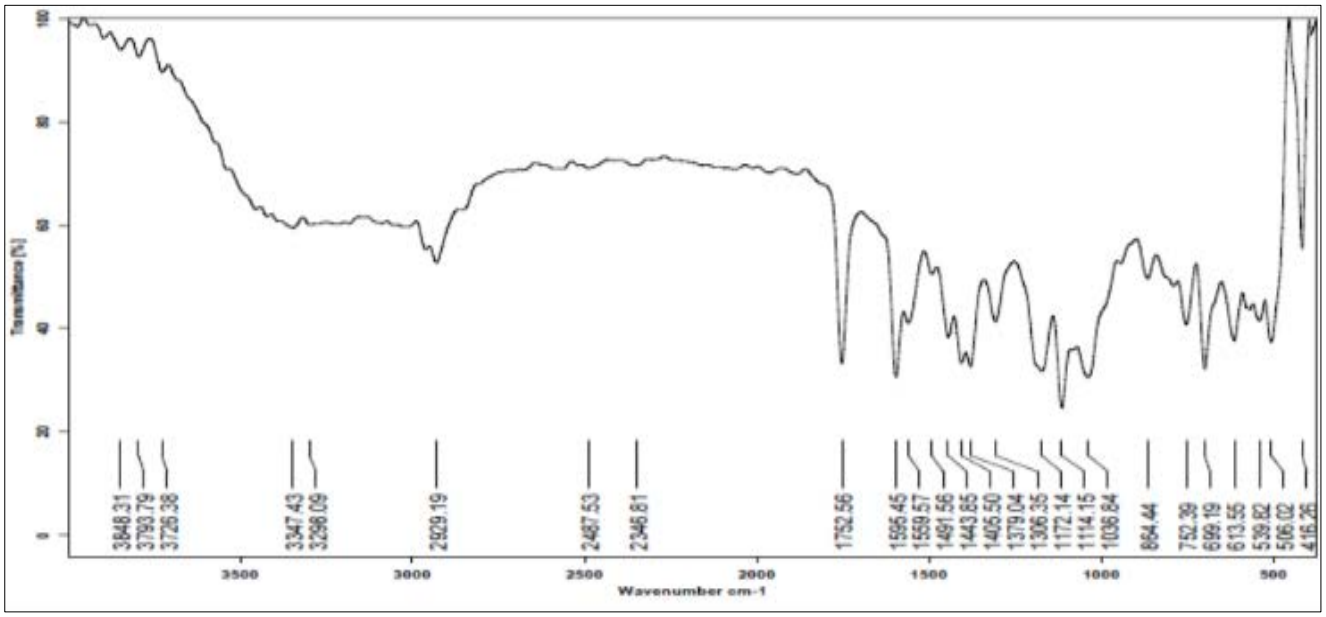

Fig 3: FTIR spectra of drug and β-cyclodextrin

Table 6: Interpretation of pure drug and β-cyclodextrin functional groups and characteristic absorption

S. No	Functional group	Characteristic absorption wave number (cm^{-1})
1.	- C=O (Acid group)	1752.56
2.	- CH_3 (Methyl group)	1379.04
3.	- C=N(Pyrimidine structure)	1491.56
4.	-C - O - C-	1172.14
5.	-O-H	3347.43

Discussion

There is no change in the nature and position of the characteristic band for the drug and drug-carrier used in the formulation, it can be concluded that there is no chemical interaction between the drug and carrier.

Standard curve of ambrisentan

Series of concentrations and their absorbance are as shown in Table 7. Calibration curve of Tinidazole is as shown in Figure 4.

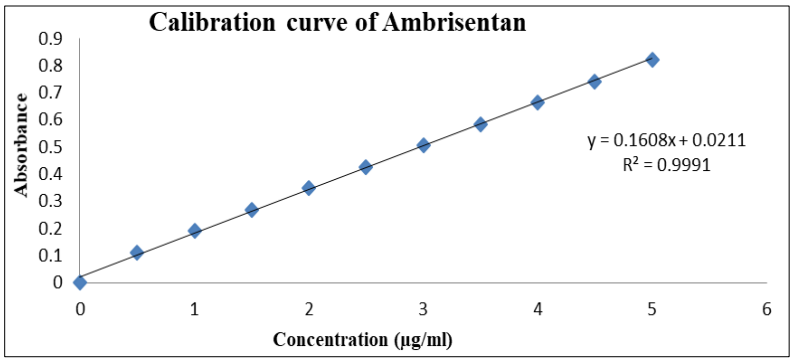

Fig 4: Calibration curve of ambrisentan

Table 7: Series of concentrations and their absorbance

Concentration (µg/ml)	Absorbance
0	0
0.5	0.110
1	0.189
1.5	0.268
2	0.347
2.5	0.426
3	0.505
3.5	0.584
4	0.663
4.5	0.742
5	0.821

Discussion

Based on above results, it has been inferred that API shows linearity in concentration range of 0.5-5µg/ml. the regression coefficient of calibration curve was found to be 0.9991.

In vitro dissolution

Dissolution data and comparative studies of all physical mixture are shown in Table 8. Dissolution profiles of all physical mixture P1to P8 are shown in Figure 5.

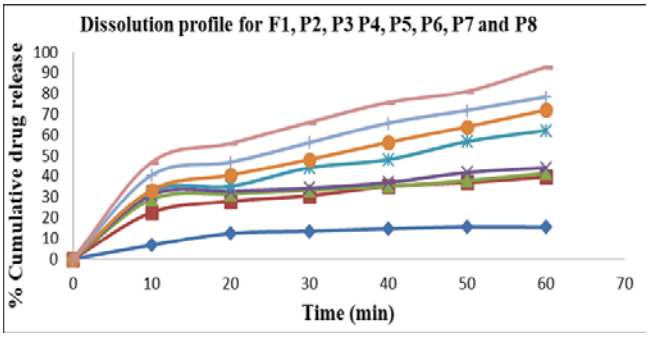

Fig 5: Comparitive profile of all physical mixture P1to P8

Table 8: Dissolution data and comparative studies of all physical mixtures

S. no	Time	P1	P2	P3	P4	P5	P6	P7	P8
1.	0	0	0	0	0	0	0	0	0
2.	10	6.78	22.52	28.82	32.79	8.59	33.33	40.54	46.84
3.	20	12.4	27.92	32.79	35.13	17.01	40.54	46.84	55.85
4.	30	13.5	30.63	34.23	27.269	44.14	48.10	56.21	66.12
5.	40	14.68	35.13	36.93	35.56	48.10	56.39	65.76	75.67
6.	50	15.6	36.93	41.80	45.71	56.75	63.96	71.89	81.08
7.	60	16.0	39.63	41.44	55.014	62.16	72.07	78.37	92.79

Discussion

Increase in concentration carrier such as the β-cyclodextrin increased in drug release. Higher the amount of carrier greater is the driving force to release the drug. This is because increase in carrier concentration increased the solubility of drug from the physical mixture is increased.

Optimization of physical mixture from dissolution data

For optimization of physical mixture Comparative studies of Pure drug (P1) with physical mixtures P7 and P8 are shown in Table 9. Dissolution profile for Pure drug (P1) with physical mixtures P7and P8 are shown in Figure 6.

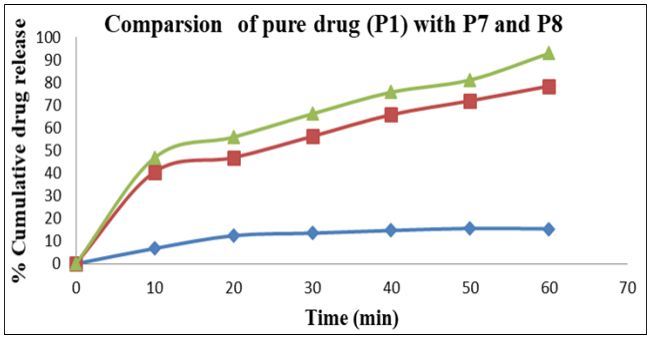

Fig 6: Dissolution profile for Pure drug (P1) with physical mixtures P7and P8

Table 9: Comparative studies of Pure drug (P1) with physical mixtures P7 and P8

S. No	Time	P1	P7	P8
1.	0	0	0	0
2.	10	6.78	40.54	46.84
3.	20	12.4	46.84	55.85
4.	30	13.5	56.21	66.12
5.	40	14.68	65.76	75.67
6.	50	15.6	71.89	81.08
7.	60	16.0	78.37	92.79

Discussion

The concentration of β-cyclodextrin used in P7 and P8 is used for the formulation of immediate release dosage forms because the solubility of drug is mostly increased when it compared with the pure drug i.e., P1. The P7and P8 physical mixtures drug release is less than 75% the drug of P7 physical mixture is 78.37% and the P3 physical mixture is 92.79%. Hence, these two physical mixtures are used for preparation of immediate release dosage forms. From this comparison profile P8 physical mixture is considered as optimized formula.

Dissolution-application of kinetics

Zero order plot for optimized formula is shown in Figure 7, First order plot for optimized formula is shown in Figure 8 and Kinetic data of optimized formula (P8) are shown in Table 10.

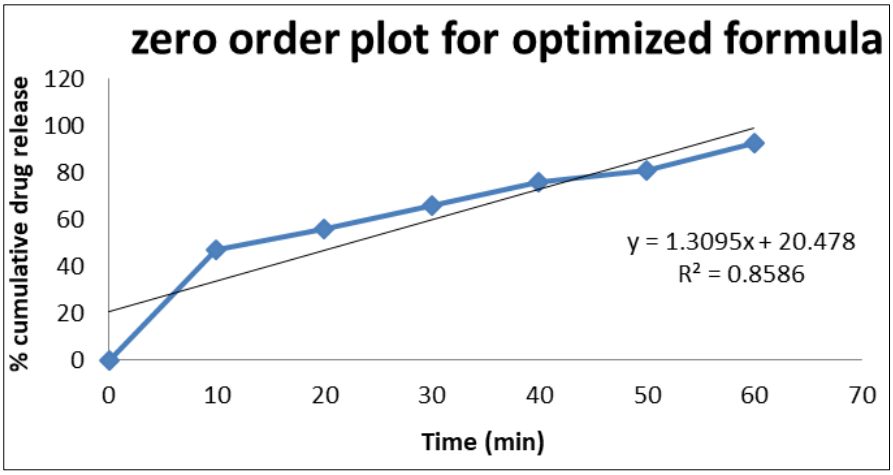

Fig 7: Zero order plot for optimized formula

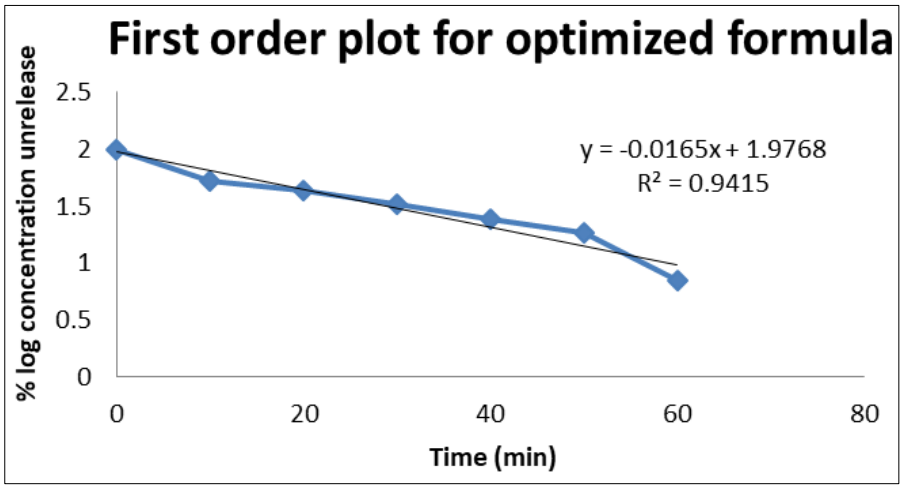

Fig 8: First order plot for optimized formula

Table 10: Kinetic data of optimized formula (F9)

PLOT	Regression R^2
Zero order plot	0.8586
First order plot	0.9415

Discussion: From the regression valve closer to unity in case of first order (R^2=0.9415) the release is apparently first order. As clearly indicated the release of the drug followed first order release kinetics and regression valve indicates fair of linearity in the data. This shows that the release is dependent on the concentration of drug. When plotted according to the zero order equation, the data indicated poor linearity as represented by regression valvesR^2=0.8586. Hence this optimized formulation is used for formulation of fast dissolving tablets.

Conclusion

We can conclude that this physical mixture was designed to enhance the drug solubility can able to formulate immediate release dosage forms with the aid of different ratio of carrier.

As per the results generated in the study, we can conclude, the release profile and kinetics of drug release for different ratio of carrier concluded as follows.

P8 > P7 > P6 > P5 > P4 > P3 > P2 > P1

Thus P8 (1:7) concentration used physical mixture attain fast release dispersion than the other concentration like P7, P6, P5, P4, P3, P2, P1.

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References

1. Singh M, Sayyad AB, Sawant SD. Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. Journal Pharmaceutical Research,2010:3(10):249-250.
2. Chiou WL, Riegelman S. Pharmaceutical application of solid dispersion system. Journal Pharmaceutical Sciences,1971:60:1281-1302.
3. Dhirendra K. Solid dispersions: A review. Pakistan Journal Pharmaceutical Sciences,2009:22(2):234-246.
4. Sheth NS. Formulation and Evaluation of solid dispersion of Olanzepine. International Journal Pharmaceutical Sciences Research,2011:2(3):691-697.

5. Okonogi S, Puttipipatkhachorn S. Dissolution improvement of high drug-loaded solid dispersion. American Association of Pharmaceutical Scientists Pharm Sci Tech,2006:7(2):E1-E6.
6. Rawat A, Verma S, Kaul M, Saini S. Solid dispersion: Astraegy for solubility enhancement. International Journal pharmaceutical technology,2011:3:1062-1099.
7. Kalia A, Poddar M. Sold Dispersion; an approach Towards Enhancing Dissolution rate. International Journal Pharmaceutical Sciences,2011:1:1-14.
8. Lachman L, Liberman HA, Kang JL. The theory and practice of industrial pharmacy,1987:(3):297-299.
9. Aulton ME. The science of dosage form design. Churchill Livingstone, 2002, (2).