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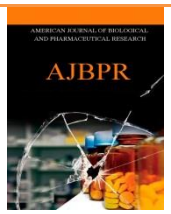

PREPARATION AND ENHANCEMENT OF SOLUBILITY OF LORATIDINE USING SOLID DISPERSION METHOD

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ABSTRACT

In the present study Loratidine solid dispersions were formulated. The enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. Loratidine was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions. The precompression blend of Loratidine solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The precompression blend of all the batches indicates good to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F1 formulation containing, Drug and Peg 4000 in the ratio of 1:0.5 showed good result that is 94.95 % in 50 minutes. As the concentration of polymer increases the drug release was decreased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F1 formulation is the better formulation.

INTRODUCTION

General introduction

From the several previous years, the pharmaceutical scientists were working to enlarge patient compliance and secure dosage forms due to improved requirement in the market for them. As a result, developing the novel technologies has been growing annually because the growth of novel drug molecule requires high cost rather than novel technology. So the current trend in the greater part of pharmaceutical industries is development of dosage form with new formulation technology using old drug molecules to improve safety, efficacy and patient compliance [1, 2]. Development of solid dispersion compacts is one such technology to enhance dissolution rate of poorly soluble drugs, thereby improving efficacy of drug molecules [2]. The most convenient and commonly employed route of drug delivery has been by oral intake. The oral route is the preferred route of drug administration due to its convenience, better patient compliance and low medicinal production costs. In order for a drug to be absorbed into the systemic circulation after oral administration, the drug must be dissolved in the gastric fluids [2]. It is well conventional that the active ingredient in a solid dosage form must undergo dissolution after it is available for absorption from the gastrointestinal tract. The absorption rate of poor water soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site,

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i.e. the dissolution rate is the rate limiting step in drug absorption [3]. The poor dissolution rate of water insoluble drugs and poorly soluble drugs is still a significant problem confronting the pharmaceutical industry. Newly developed chemical entities do not reach the market because of their poor oral bioavailability due to inadequate dissolution in G.I fluids. The active ingredient must undergo dissolution before it is available for absorption from the gastrointestinal tract. The poor dissolution characteristics of water insoluble drugs are a major challenge for pharmaceutical industries. Accordingly, many hydrophobic drugs show erratic and partial absorption from the gastrointestinal tract.

One of the major challenges in drug development nowadays is poor solubility, as estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity [4, 5]. Bioavailability of poorly water-soluble drugs is inadequate by their solubility and dissolution rate. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. The term "water-insoluble drugs" includes those drugs that are "sparingly water-soluble" (1 part solute into 30 to 100 parts of water), "slightly water-soluble" (1 part solute into 100 to 1000 parts of water), "very slightly water-soluble" (1 part solute into 1000 to 10,000 parts of water), and "practically water-insoluble" or "insoluble" (1 part solute into 10,000 or more parts of water).

BCS classification system

Based on the solubility and permeability, drugs are classified into four categories. Biopharmaceutics Classification System (BCS) was introduced by *Amidonetal*., as a basis sfor predicting the possibility of *in vitro-in vivo* correlations for immediate release dosage forms, based on the detection that drug solubility/ dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption.

The BCS was developed mainly in the situation of immediate release solid oral dosage forms. It is the scientific support for classifying drug substances based on their aqueous solubility and intestinal permeability. It is the drug development tool that allows estimation of the contributions of three major factors dissolution, solubility and intestinal permeability that affect oral drug absorption from immediate release solid oral dosage forms. It was first introduced into regulatory decision making process into guidance document of immediate release solid oral dosage forms:

Class I: High permeability and solubility
Formulation independent

The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine.
Examples: Benzapril, Loxoprofen, Sumatriptan etc.

Class II: High permeability but low solubility
Formulation dependent

The bioavailability of class II compounds is limited by drug solubility/dissolution.
Examples: Valsartan, Nimesulide, Loratadine, Aceclofenac etc.

Class III: Low permeability but high solubility
Dependent on barrier properties

The bioavailability of class III compounds is limited by intestinal permeability.
Examples: Gabapentine, Topiramate, Atropine etc.

Class IV: Low permeability and low solubility
Formulation and barrier properties dependent

The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability.
Examples: Hydrochlorthiazide, Furosemide, Meloxicam etc.

Techniques for Dissolution Enhancement

There are various techniques available to improve the solubility subsequently improves dissolution rate of poorly soluble drugs. Some of the approaches to improve the solubility and dissolution rate are

Micronization

Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Micronizationis used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Micronization of drugs is widely done by milling techniques using a jet mill, rotor stator, colloidal mill, and air attrition. But, the effect of micronization is often unsatisfactory, particularly when the drugs are encapsulated or tablet. Micronized drugs also have the affinity to agglomerate as a result of their hydrophobicity, thus reducing their available surface area. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air. It is difficult to remove or wet these particles. All these effects, in fact, reduce the rate ofdissolution [5].

Nanonization

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of several drugs that are poorly soluble in water.

Nanonization broadly refers to the study and use of materials and structures at the nano scale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it may also decrease systemic side-effects [6]. There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying etc.

Salt form

Salts have improved solubility and dissolution characteristics in comparison to the original drug. Example: Salt of basic drug like Atropine is more soluble than parent drug. Salt formation may increase hygroscopicity leading to stability problems. Solubilization technique lead to liquid formulations that is typically unattractive from patient acceptability and commercialization.

Use of surfactants

Solubilization enhanced by using surfactants, to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearate and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-benzyl-Laspartate), b-poly (ethylene oxide) etc., used as carrier for solubility and dissolution enhancement .Improvement of drug solubility by using the amphiphilic surfactants is due to lowering of surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. To get some significant solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration (CMC). The CMC will depend upon the surfactant itself and the ionic strength of the media. The amount of surfactant required depends on the CMC and the degree to which the compound partitions into the surfactant micelles but the solubilization of drugs in aqueous media by the use of surfactants leads to liquid formulations that are generally less patient acceptability and commercialization.

Use of Co-solvents

Co-solvent is a highly effective technique for enhancement of solubility of poorly soluble drugs. It is well-known that the addition of an organic co-solvent to water can significantly change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be enhanced by changing polarity of the solvent. This can be achieved by addition of another solvent. This process is known as co-solvency. Solvent used to increase solubility is known as co-solvent. Co-solvent system mechanism is reducing the interfacial tension between the aqueous solution and hydrophobic solute. The use of mixed solvent system is frequently necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols, dimethylsulfoxide, ethanol and N, N dimethyl formamide can be used[6]but the solubilization of drugs in inorganic solvents or in aqueous media by the use of co solvents leads to liquid formulations that are generally less patient acceptability and commercialization.

Use of Metastable Polymorphs

The presence of metastable, polymorphic crystalline forms can exert a great influence on the solubility, dissolution rate, and biological activity of medicaments. The separation and selective use of a definite polymorphic form to have the highest solubility, is a technique that can be useful in certain cases for the increase of dissolution rates. Melting followed by rapid cooling or recrystallization from different solvents can produce metastable forms of a drug. For example, a metastable form of chloramphenicol palmitate is more water-soluble than the A and C forms.[7]

Aim of study

The main aim of this study is to Preparation and enhancement of solubility the Loratidine by solid dispersion method and formulated as fast dissolving tablets.

Objectives

- To enhance the aqueous solubility of Loratidine by suitable solid dispersion technique.
- To develop analytical profile of Loratidine.
- To formulate solid dispersions by solvent evaporation method using methanol as solvent.
- To carry out drug excipient compatibility studies by using FTIR.
- To carry out following evaluation parameters

A) Angle of repose
B) Bulk density
C) Tapped density
D) Compressibility index

- To carry out following evaluation parameters

E) Weight variation
F) Friability
G) Thickness & Diameter
H) Hardness
I) Disintegration test
J) *In vitro* Dissolution test

Drug Profile

K) **Name** : **Loratadine**

L) **Description** :

Loratadine is a derivative of azatadine and a second-

Development

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Loratidine dose was taken as 10mg.Water soluble polymers such as PEG 4000 and PEG 6000 were selected as carriers. Methanol used as solvent. Here used Technique is Solvent Evaporation Solid Dispersion. Drug and polymers were taken in different ratios stated in the formulation chart (Table 2). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dipersions were mixed with required quantities of diluent, lubricant and glidant. The blend was evaluated for precompression parameters.

Evaluation of tablets

Pre compression parameters

Measurement of Micromeritic Properties of Powders

Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation [7].

Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula.

Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula [8].

Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation [9].

Post compression parameters

Thickness

The thicknes of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

Percentage friability was calculated using the following equation.

Assay

The content of drug carried out by take five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in pH 6.8 phopshate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 282 nm using UV sectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

Dissolution test of Loratidine tablets

Drug release from Loratidine tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 500 ml. The whole

study is being carried out at a temperature of 37^0 C and at a speed of 50 rpm. 5ml aliquots of dissolution media were withdrawn each time at suitable time intervals and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

RESULTS & DISCUSSION

Determination of λ max

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 282 nm.

Calibration curve of Loratidine

The standard curve of Loratidine was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 6.8 phosphate buffer.
The standard graph values of Loratidine are tabulated as below -

Drug – Excipient Compatibility Studies By FTIR Studies

Loratidine was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions.

Evaluation

Characterization of Precompression Blend

The precompression blend of Loratidine solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Evaluation of Tablets

Physical Evaluation of Loratidine solid dipersion tablets

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 7.All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.6 to 5 kg/cm^2 and the friability values were less than 0.561% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.71-4.91cm. All the formulations satisfied the content of the drug as they contained 98-100% of Loratidine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits

In-vitro release studies

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hrs and analysed after appropriate dilution by using UV Spectrophotometer at 282nm.

Among all the formulations F1 formulation containing, Drug and Peg 4000 in the ratio of 1:0.5 showed good result that is 94.95 % in 50 minutes. As the concentration of polymer increases the drug release was decreased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F1 formulation is the better formulation. The formulation containing combination of PEG 4000& 6000 was also not producing desired percentage drug release. finally concluded that F1 formulation is considered as optimised formulation.

Table 1. Formulation table showing various compositions

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loratidine	10	10	10	10	10	10	10	10	10
PEG 4000	5	10	15	20	-	-	-	-	10
PEG 6000	-	-	-	-	5	10	15	20	10
Polyplasdone XL	30	30	30	30	30	30	30	30	30
Aerosil	5	5	5	5	5	5	5	5	5
Manesium stearate	5	5	5	5	5	5	5	5	5
MCC	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s

Total weight of tablets = 100 mg
The tablets were prepared by using 6 mm flat surfaced punch. The hardness of the tablets was maintained as 2.5 kg/cm^2.

Table 2. Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35

Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

Table 3. Scale of Flowability

Compressibility Index (%)	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table 4. Standard Graph values of Loratidine

Conc [µg/ml]	Abs
0	0
5	0.178
10	0.345
15	0.503
20	0.653
25	0.812

Table 5. Physical properties of precompression blend

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	26.15°	0.53	0.58	10.13	1.12
F2	27.12°	0.58	0.63	10.34	1.17
F3	26.40°	0.51	0.61	10.11	1.16
F4	25.31°	0.59	0.64	10.12	1.11
F5	25.43°	0.54	0.64	9.40	1.10
F6	25.41°	0.54	0.58	10.01	1.13
F7	26.10°	0.54	0.61	10.20	1.13
F8	26.11°	0.56	0.63	9.93	1.13
F9	25.10°	0.53	0.59	9.43	1.03

Table 6. Physical Evaluation of Loratidine tablets

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity(%)
F1	100	4.76	2.5	0.420	99.44
F2	98	4.74	2.2	0.341	98.84
F3	97	4.71	2.6	0.363	100.09
F4	104	4.80	2.8	0.561	100.34
F5	95	4.81	2.8	0.482	99.23
F6	100	4.74	2.4	0.513	97.35
F7	104	4.76	2.5	0.412	98.94
F8	99	4.71	2.6	0.432	99.48
F9	100	4.73	2.5	0.512	100.03

Table 7. Invitro dissolution data for formulations.

Time(MIN)	% Drug release			
	F1	F2	F3	F4
0	0	0	0	0
5	26.73	16.73	12.56	7.73
10	31.06	20.4	16.57	11.56
20	44.9	25.9	18.9	16.56
30	57.06	35.56	27.73	18.9
40	75.56	44.9	42.4	22.73
50	94.9	54.4	47.9	36.06
60		79.9	66.56	48.4

Table 8. Invitro dissolution data for formulations

Time(MIN)	% Drug release			
	F5	F6	F7	F8
0	0	0	0	0
5	11.86	8.18	9.21	7.51
10	19.01	11.86	12.60	10.90
20	26.16	16.06	16.43	15.55
30	28.22	21.44	24.83	23.80
40	36.99	29.62	31.32	30.29
50	58.81	59.77	37.95	31.98
60	73.55	65.59	40.90	37.58

Table 9. Invitro dissolution data for formulations

Time(MIN)	% Drug release
	F9
0	0
5	7.51
10	10.90
20	15.55
30	23.80
40	28.29
50	34.98
60	39.58

Fig 1. Standard Curve of Loratidine

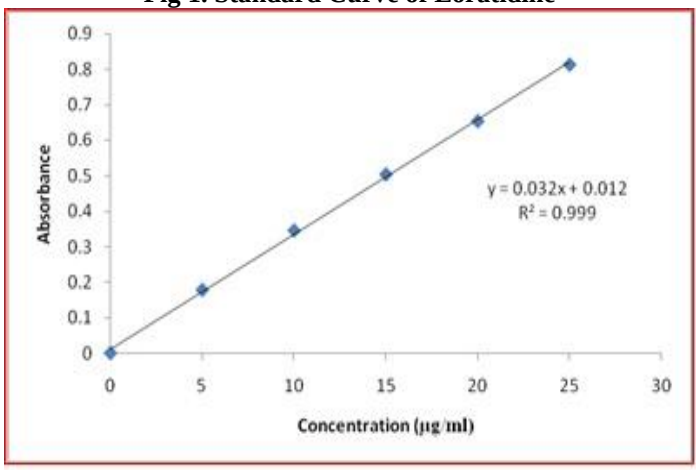


Fig 2. FTIR spectra of pure drug

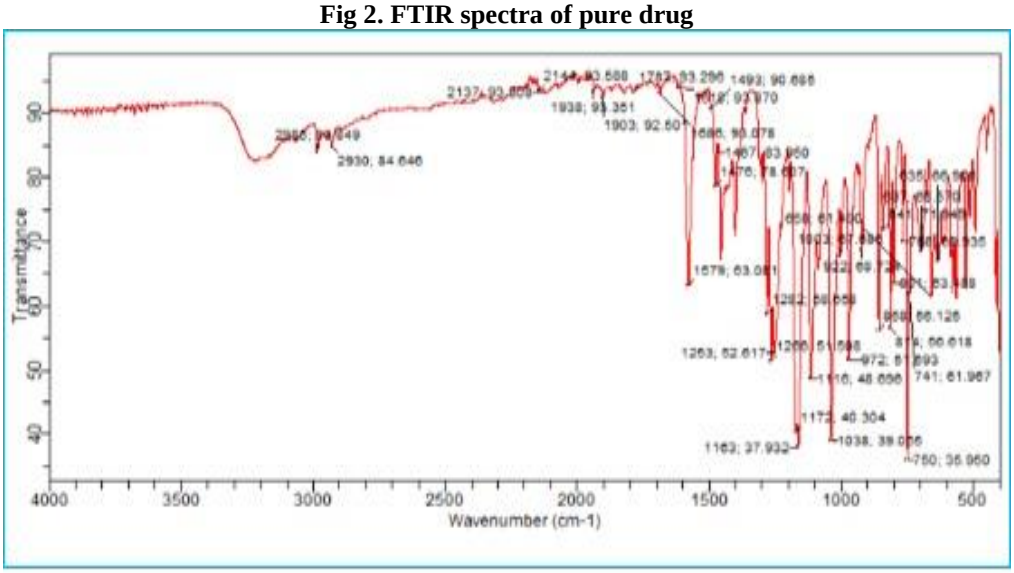


Fig 3. FTIR spectra of optimised formula

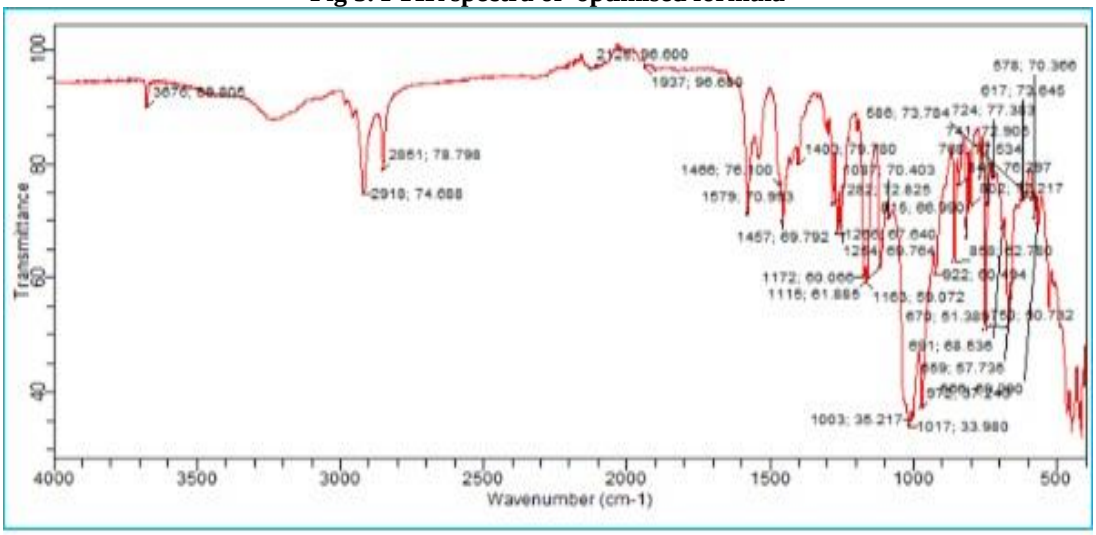


Fig 4. *In vitro* dissolution data for formulations

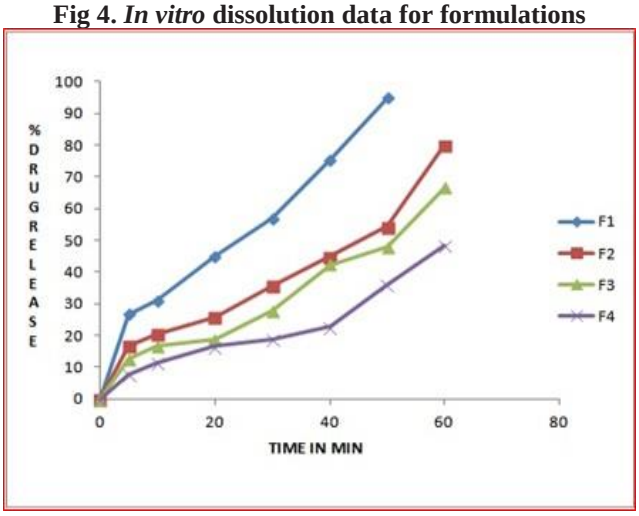


Fig 5. Invitro dissolution data for formulations F5– F8 by using PEG 4000 Polymer

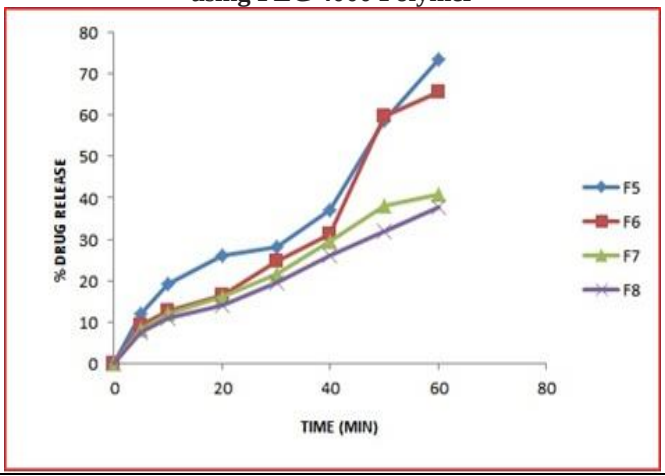
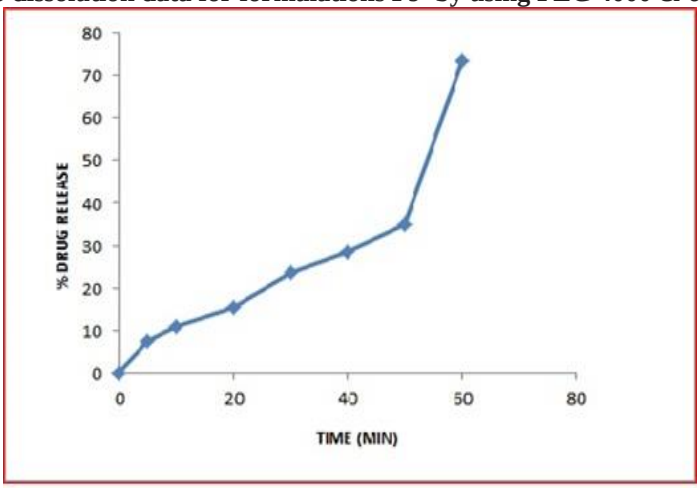


Fig 6. Invitro dissolution data for formulations F9 by using PEG 4000 & 6000 Polymer



CONCLUSION

Loratidine belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. The standard curve of Loratidine was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 6.8 phosphate buffer. Loratidine was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions.

The pre-compression blend of Loratidine solid dispersions were characterized wit- h respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The pre-compression blend of all the batches indicating good to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets.The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests.Among all the formulations F1 formulation containing, Drug and Peg 4000 in the ratio of 1:0.5 showed good result that is 94.95 % in 50 minutes. As the concentration of polymer increases the drug release was decreased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F1 formulation is the better formulation.

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Nil

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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