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Approaches for Solubility enhancement of Floroqunilones(Second Generation) during Scale Up Procedures

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Abstract : Poor dissolution descriptions of water-insoluble drugs are a chief limitation in drug bioavailability and often pose a problem to scientists. Several techniques for solubility enhancement have been tried in this context. Solid dispersion technology is one such technique. Though, there was an excessive attentiveness in solid dispersion technology during the past times to increase solubility of poorly water-soluble drug, their lucrative use has been partial, because of manufacturing and stability problems. In the current work two such approaches were tried i.e., solvent evaporation and melting method. In solvent evaporation method, the drug was combined with lactose & mannitol and in melting method drug was combined with polymer PEG-6000. The % yield by these techniques was 88.1% and 94.5% respectively. These dispersions when formulated as tablets yielded tablets with good oval appearance, dissolution rate, solubility and stability.

Keywords : Solid dispersion, Solubility, Solvent evaporation, Melting method, Stability.

Introduction

Fluoroquinolones are one of the utmost favorable and vigorously followed areas of current anti-infective chemotherapy portraying broad spectrum and effective activity. They have a comparatively simple molecular nucleus, which is responsive to many structural alterations. These have numerous approving properties such as excellent bioavailability, good tissue penetrability and a relatively low regularity of adversative and toxic effects. They have been found operative in treatment of several infectious diseases. Fluoroquinolones are new class of synthetic antibiotics with potent bactericidal, broad spectrum activity in contradiction of countless clinically vitalpathogens[1]. The second-generation Fluoroquinolones have augmented gram-negative activity, as well as some gram-positive and atypical pathogen coverage. These drugs have wider clinical applications in the treatment of complicated urinary tract infections, sexually transmitted diseases, selected pneumonias, skin infections, etc[2]. In the era of research and development, plenty of techniques are developed for solubility enhancement of poorly soluble drugs but these techniques often have some limitations like scale up, cost effectiveness, instability, biocompatibility, toxicity, regulatory requirements etc.

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The objective of our work was to make a suitable solid oral dosage form responsible for solubility enhancement which can overcome the above-mentioned problems of second generation drugs via solid dispersions using solvent evaporation and melting method. Also, the research work includes the study of physicochemical properties and in vitro drug release profile of the developed solid dispersions[3, 4].Theseboth methods can attain therapeutically operational concentration of the drug in the systemic circulation over an extended period of time with better patient compliance, enhanced drug release and solubility[5, 6]. Water soluble carriers are commonly used to produce a controlled release formulation. The properties of the carriers have major influences on the release profile of the drug. These carriers include lactose, mannitol (ratio: 1:1, 1:2 & 1:4) and PEG-6000 (1:3, 1:6 &1:9).

Materials and Methods

The drug and all other chemicals used as excipient are obtained as a gift sample from m/s Arbro Pharmaceutical Private Limited, New Delhi. All other chemicals were of analytical reagent grade,ultra violet (UV) spectrophotometer (Shimadzu Corp.).

Calibration curve of Pure Drug

The solution was prepared by dissolving 100mg of drug in few ml of methanol in a 100ml volumetric flask and then volume makeup of solution was done up to the mark using 0.1N hydrochloric acid for attaining the solution of strength 1000 µg/ml[7-9]. Dilutions of 2, 4, 6, 8, 10 µg/ml of solution were prepared and volume made up to 10 ml by using 0.1N HCl[10]. The maximum absorption was observed at 276nm with linearity range of 2-10µg/ml. A calibration curve was plotted against absorbance vs concentration that obeyed Beer's Lambert's law (Fig. 1)

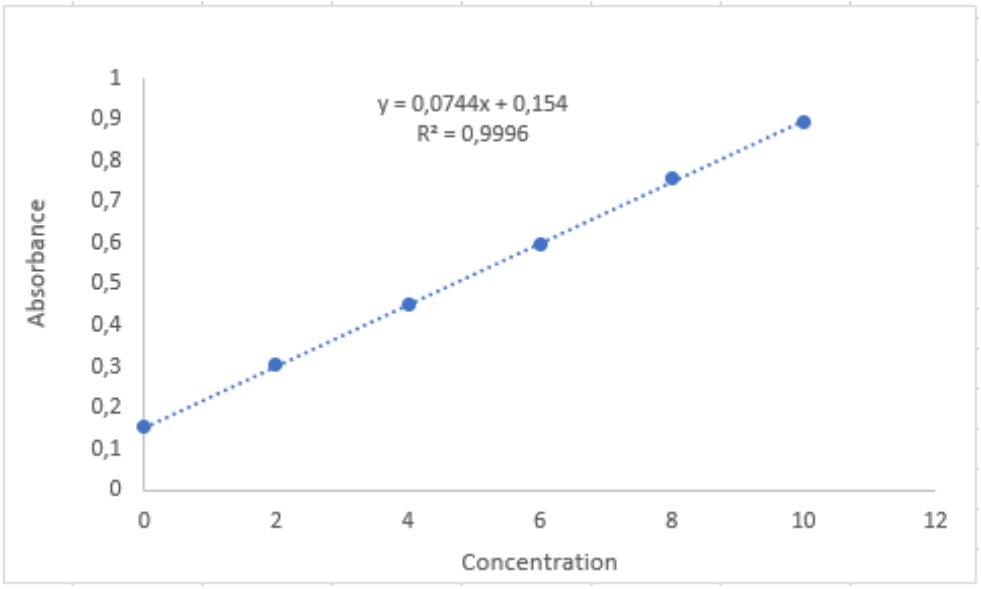


Fig1: Calibration Curve of Pure Drug

Preparation of Solid Dispersion

By Solvent Evaporation Method:

An excess amount of drug was added to 10 ml of aqueous solution of water soluble carriers like Mannitol & lactose in the various ratios such as 1:1, 1:2 & 1:4 in screwed capped bottles. Samples were shaken in an orbital shaker for the 24 hrs. at room temperature[11]. Then, the suspensions were filtered through a Whatman filter paper grade no. 1. Filtered solution were diluted suitably with distilled water. The drug & carrier was dissolved in dichloromethane & triturated in dry mortar until the solvent evaporated & a clear film of drug & carrier was obtained. The resultant solid dispersion was scrapped out with a spatula and were again

pulverized in mortar & pestle & passed through a sieve no. 80. The preliminary solubility analysis was carried out in UV spectrophotometer at 276 nm which can be seen inTable 1[12]

Table 1: Solubility of Solid Dispersions by using Carriers (Lactose and Mannitol)

Drug and Carrier		**Solubility (µg/ml)**	
Pure Drug		4.8	
Drug: Mannitol Ratios	Drug: Lactose Ratios	Drug: Mannitol	Drug: Lactose
1:1	1:1	9.65	21.64
1:2	1:2	12	29.33
1:4	1:4	15.24	32.87

By Melting Method:

Solid dispersions of drug were prepared by melting the polymer (PEG-6000) at 60°C, succeeded by addition of required amount of drug. The molten polymer and drug were stirred and immediately cooled in an ice bath. The obtained solidified mass was crushed in mortar pestle and passed through sieve #40 and then stored in the desiccator. The preliminary solubility analysis was carried out in UV at 276 nm that can be seen in Table 2[13].

Table 2: Solubility of Solid Dispersions by using Polymer PEG-6000

S.No.	**Drug and PEG-6000**	**Solubility (µg/ml)**
1.	Pure Drug	4.8
2.	1:3	18.27
3.	1:6	30.18
4.	1:9	25.28

Tablet Formulations

By Solvent Evaporation Method:

On the basis of UV spectrometric analysis in solubility enhancement technique, the best ratio for drug: lactose was 1:4. Hence drug prepared with lactose in ratio of 1:4 equivalent to Drug and Microcrystalline Cellulose-Plain (MCC-P as diluent)were accurately weighed, mixed properly and passed through sieve #40. The required amount of starch (binder) and water is added until a thick paste is formed, heated at 100 degrees and allowed to cool at room temperature. After kneading into a dough, it was passed through a sieve to form granules Magnesium stearate (lubricant), Aerosil-200 (glidant) and Crospovidone (disintegrant) were accurately weighed and added to granules[14] and then compressed to form Tablets.

In the present work, four formulations (S1 to S4) of second generation fluoroquinolones tablets were prepared using each of the excipient in different concentrations as shown in the Table.3.

Table 3: Formulation Composition of Second Generation Floroquinolones Tablets (Drug: Lactose- 1:4)

Ingredients	**F1**	**F2**	**F3**	**F4**
Solid dispersion equivalent to drug	300 mg	300mg	300mg	300mg
MCC-P	75mg	65mg	75mg	80mg
Starch	55mg	55mg	45mg	85mg
Aerosil-200	20mg	25mg	25mg	2.5mg
Crospovidone	30mg	35mg	30mg	30mg
Magnesium Stearate	20mg	20mg	25mg	2.5mg

By Melting Method:

On the basis of UV spectrometric analysis in solubility enhancement technique, the best ratio for drug: PEG-6000 was 1:6. Hencethe drug was prepared with PEG-6000 in ratio of 1:6 equivalent to drug and then formulated into tablets.

Four formulations (M1 to M4) of second generation fluoroquinolones tablets were prepared using each of the excipient in different concentrations as shown in the Table.4.

Table 4: Formulation Composition of Second Generation Floquinolones Tablets (Drug: PEG-6000- 1:6)

INGREDIENTS	F1	F2	F3	F4
Solid dispersion equivalent to drug	300 mg	300mg	300mg	300mg
MCC-P 101	40mg	35mg	45mg	50mg
Starch	44mg	42mg	35mg	40mg
Aerosil-200	2mg	3.2mg	7.5mg	2.5mg
Crospovidone	12mg	15mg	7.5mg	5mg
Magnesium Stearate	2mg	3.8mg	5mg	2.5mg

Dissolution Studies of Tablets

For this test USP dissolution apparatus was used. All the above formulations ranging from S1 to S4 and M1 to M4 were placed in each vessel (6 vessels) containing 900 ml of 0.1 M hydrochloric acid (HCl) as a dissolution medium maintained at 37 ± 0.5 °C. The rotational speed of the apparatus was held constant at 50 rpm. A sample of 5 ml was withdrawn at a fixed time intervals (5, 10, 15, 20 and 30min) and this was immediately replaced with the same volume of fresh test media [15]. The withdrawn sample was analyzed spectrophotometrically at 276 nm, using 0.1 M HCl as blank. The percentage of drug release was noted that is given in Table 5 and 6. S2 and M1 formulations were chosen as the best formulation on the basis of their thickness, hardness, flow properties and percentage drug release. Stability studies were conducted for these formulations.

Table 5: In-Vitro Dissolution Study (% Release of Drug) of S2 Formulation

Time (Min)	F1	F2	F3	F4
5	35.67%	74.33%	64.89%	51.64%
10	50.26%	83.41%	75.12%	63.22%
15	74.12%	92.65%	84.65%	71.30%
20	85.37%	97.05%	90.55%	72.08%
30	90.32%	99.68%	92.25%	77.18%

Table 6: In-Vitro Dissolution Study (% Release of Drug) of M1 Formulation

Time (Min)	F1	F2	F3	F4
5	44.25%	18.91%	17.5%	37.67%
10	79.55%	63.54%	37.7%	62.26%
15	89.19%	72.28%	55.55%	74.12%
20	96.36%	85.18%	69.13%	89.37%
30	98.47%	87.64%	85.23%	95.32%

Stability Studies

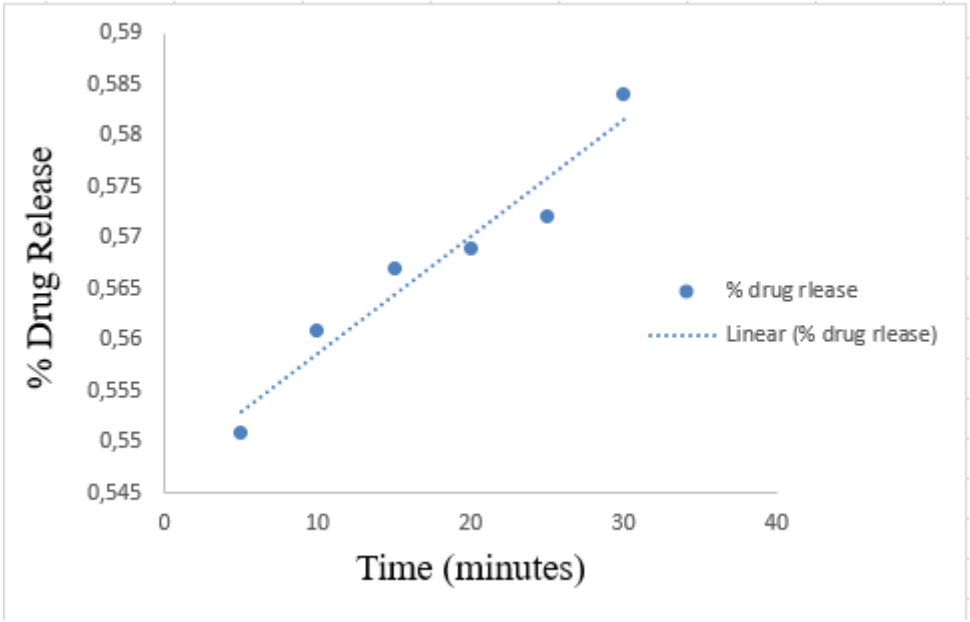
The accelerated stability studies were conducted according to ICH and WHOguidelines161. Both the optimized tablet formulation S2 and M1formulated by solvent evaporation and melting method respectively (20

tablets from each formulation) were stored at 40 °C ± 2 °C /75% ± 5% RH in a stability chamber for a period of 3 months. The dispersions were analyzed for change in physical appearance and percentage drug release after a period of 0, 30, 45, 60, 90 days.

Results and Discussion:

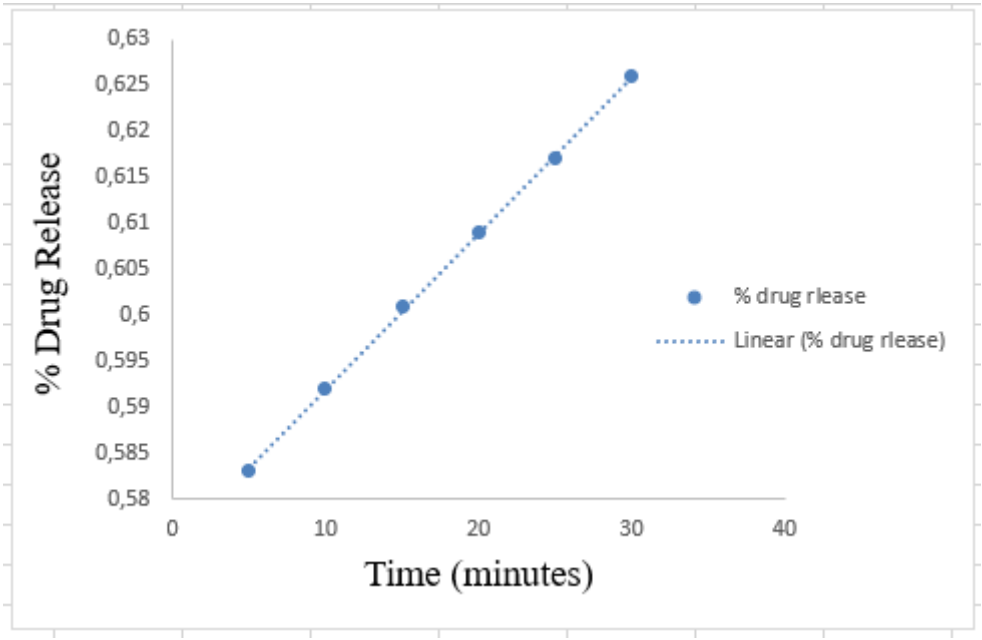
The existing analysis was piloted to develop the dissolution and solubility of second generation fluoroquinolones using solid dispersions formulation by solvent evaporation and melting method with different ratios of lactose & mannitol and PEG-6000 respectively. The maximum absorption of pure drug was observed at 276nm(Fig. 1) and the solubility of pure drug was found to be 4.8 µg/ml.

Both techniques exhibited improved dissolution rate and solubility of drug to a great extent. In solvent evaporation method, thebest drug: lactose ratio (1:4) was chosen on the basis of highest solubility parameter which was found to be32.87 µg/ml as compared to other ratios with lactose and mannitol. This drug: lactose ratio (1:4) when formulated into tablet exhibited a percentage release of88.1%in formulation S2. Whereas, in melting method, drug and polymer PEG-6000 ratio 1:6showed highest solubility of 30.18µg/ml and percentage drug release of 94.5%in formulation M1. The percentage drug release of tablets formulated by solvent evaporation and melting method for S2 and M1 can be seen in fig 2 and fig 3 respectively.The results of stability studies of optimized tablet formulation S2 and M1 by both methods showed no changes in physical appearance as well as in percentage drug release during storage period of 3 months. Finally,it could be concluded that both these techniques have remarkable potential in controlled release dosage form and can be taken for pilot scale batches.



% Drug release is 88.1% i.e.within the range of 85-90%

Fig 2: Percentage Drug Release of S2 Formulation



% Drug release is 94.5% i.e. above the range of 85-90%.

Fig 3: Percentage Drug Release of M1 Formulation

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