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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF NARATRIPTAN USING SUBLIMATION TECHNIQUE

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ABSTRACT:

Orodispersible Tablets (ODT) of Naratriptan a typical anti migraine is highly appropriate, as it has ease of administration for patients who are mentally ill, disabled and uncooperative. It has better patient's acceptance and compliance and other improved biopharmaceutical properties and efficiency compared with conventional oral dosage forms.

In the present research work an attempt was made to design ODT by using sublimation method by addition of camphor as subliming agent, followed by effect of lubricants were resulted. The experiment was run with six batches containing different concentrations of subliming agents. On comparing all the batches of sublimation method SF4 shows higher dissolution rate was resulted due to rapid diffusion or porous nature of tablet. Among them camphor 5% is better subliming agent for formulation of ODT of Naratriptan. Vacuum drying employed to remove sublime salts at low temperature 40ºC for 2 hr. From the results of study we concluded that formulation SF4 (Mannitol, lactose monohydrate, Crospovidone, Aspartame Sodium starch glycolate, Magnesium stearate, Orange flavor Camphor) possesses good disintegration and dissolution rate profile. An FTIR studies reveal that there is no interaction of drug with excipients. The sublimation method can be used to prepare ODTs of several categories of drugs, which need rapid onset of action. Hence sublimation method of preparing tablet with a view of obtaining faster action of drug and would be advantageous in comparing to the currently conventional forms.

Keywords: *Orodispersible tablets, Naratriptan, FTIR.*

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INTRODUCTION:

The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, an orally disintegrating tablets as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"

The concept of oral drug delivery system emerged from the desire to provide patients with conventional means of talking their medication. The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which means "Orodispersible tablet" as a tablet to be placed in the mouth where it disappears rapidly before swallowing [1].

Orodispersible tablets are also called as Orally disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts [2].

Over a decade, the demand for development of ODTs has enormously increased as it has significant impact on the patient's compliance. Orally disintegrating tablets offer an advantage for population who has difficulty in swallowing. It has been reported that Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motion sickness complications [2].

To overcome this problem, scientists have developed innovative drug delivery system known as ODTs. These are novel types of tablets disintegrates/dissolve/disperse in saliva. Their characteristic advantages such as administrating without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient's compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market [3]. Orodispersible tablets are also applicable when local action in them mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, recent advances in novel drug delivery system (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance.[9]

Sublimation has been used to produce ODTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of Sublimation upon removal of the volatile ingredients high porosity is achieved due to the formation of many pores where subliming particles previously existed in the compressed tablets prior to sublimation. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane) has been used for this purpose solvent such as cyclohexane and benzene were also suggested for generating the porosity in the matrix. Vacuum drying is the technique employed to remove the sublime salt at low temperature.

MATERIALS AND METHOD:

Materials:

Naratriptan was obtained as gift sample from Orchid Indian ltd, (Chennai, India). Croscarmellose sodium, Crospovidone, Microcrystalline cellulose, Camphor, was obtained from SD fine chemical Ltd, Mumbai, India. All other chemicals, solvents and reagents were used of either pharmaceutical or analytical grade.

Method:

Procedure for Sublimation Technique

Accurately weigh Naratriptan hydrochloride, fillers, super disintegrants, sublimating agent, sweetener and flavor. Mix Naratriptan Hydrochloride part quantity of filler and co-sift through ASTM #60 Sift remaining quantity of filler, superdisintegrants, sweetener and flavor through ASTM#40. Sift subliming agent through ASTM #100. Blend sifted materials together for 5 min. Weigh and sift magnesium Stearate through ASTM # 40. Lubricate the blend with sifted magnesium Stearate for 2 min. Compress the above blend in CEMACH Mini Rotary tableting Machine using 8mm concave punches, upper punch embossed with 'c' The prepared tablets were subjected to vacuum drying in vacuum oven at 40ºC for 2 hr.

Evaluation of Powder Blend

Precompression Parameters

Prior to compression into tablets, the blend was evaluated for properties such as:

Angle of Repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted that the tip of the funnel touches tip of the heap of the granules. The granules were allowed to flow freely through the funnel onto the surface. The diameter of the granular cone was measured and angle of repose was calculated using formula given below [14].

$\theta = \tan^{-1}(h/r)$ Where, h and r are the height and radius of the cone.

Carr's Compressibility Index

The simplex way of measurement of the free flow of

powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (I) which is calculated by using the given formula [14]

CI (%) = (TD - PD) X 100 / TD

Where,

CI = Carr's compressibility index
TD = Tapped Density

PD =Poured Density

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula [14]

Hausner Ratio = TD/PD

Where,

TD = Tapped Density,

PD = Poured density.

Tapped Density

Tapped density is the ratio between mass of granules and volume of the granules after tapping is done. It is expressed by gm/cc [15].

Tapped Density = Weight of granules/ Tapped volume

Evaluation of Post Compression Parameters:

The formulations were evaluated for hardness, weight variation, thickness, friability, disintegration time, *in vitro* dispersion time, wetting time and water absorption ratio, assay, content uniformity and *in vitro* dissolution results were shown in table 2,3and figures 1-6 [17].

a) Hardness Test:

Tablets require a certain amount of hardness and resistance to friability to withstand mechanical shock in manufacture, packing and shipping. To perform this test tablets were placed between two anvils, force to the anvils and the crushing strength that just causes the tablets to break was recorded. Monsanto hardness tester was used to measure the hardness of tablets. Six tablets from each batch were used for hardness studies and results were expressed in kg/cm^2.

b) Weight Variation Test

Randomly, twenty tablets are selected during compression and the mean weight was determined none of the tablets should deviated from the average weight by more than ±10%

c) Thickness

Tablet thickness can be measured using a simple procedure tablets were randomly selected from each formulation and their thickness was measured using Varnier calipers. The thickness was measured by placing a tablet between two arms of the Varnier calipers. This is expressed in mm.

d) Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm/min for 4min dropping the tablets at distance of 6 inches with each revolution. Pre weighed sample of 20 tablets were placed in the friabilator. Tablets were de- dusted and reweighed [18, 19, 20].

The percent friability was measured using the formula:

Friability = Initial weight-Final weight/Initial weight x 100

e) Disintegration Time

The *in-vitro* disintegration time was determined using disintegration test apparatus. Six tablets were placed in each of the six tubes of the apparatus. The basket with the bottom surface made of a stainless steel screen (mesh no.10) was immersed in water bath at 37±2^{o}C the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds [21].

f) In vitro Dispersion Time

In-vitro dispersion time was measured by dropping a tablet in measuring cylinder containing 6 ml of water six tablets from each formulation were randomly selected and *In-vitro* dispersion time was performed [22].

g) Wetting Time &Water Absorption Test

Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting time is an important step for disintegration process to take place. A piece of tissue paper folded twice was placed in a small Petridis (internal diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^{0}C [23].

The same procedure was repeated for determining water absorption ratio. The wetted tablet was then weighed. Water absorption ratio, R, was determined according to following equation [24].

$$R = \{(W_a - W_b)/ W_a\} X100$$

W_a = Weight of tablet before study.
W_b = Weight of tablet after study.
R = water absorption ratio.

h) Assay [9]
20 tablets were weighed and triturated. The tablet triturate equivalent to 1.11mg of the drug was weighed accurately dissolved in 0.1 N HCL and diluted to 100ml with 0.1 N HCL and assayed individually at respective λ max against the reagent blank. The drug content should be within 90% to 110% of the labeled claim.

i) Uniformity of Dosage Units [10]:
Uniformity of dosage units is defined as the degree of uniformity in the amount of drug substance in each unit.

j) *In vitro* Dissolution Studies [12]
The release rate of Naratriptan hydrochloride from Orodispersible tablets was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 500ml of 0.1N HCL at 37±5ºC at 50 rpm. A sample of 2ml of the solution was withdrawn from the dissolution apparatus every 5 min. for 15 sec and the sample were replaced with fresh dissolution medium. The samples were filtered through watmann filter paperno.41. Absorbance of their solution was measured at 222nm using UV spectrophotometer.

Infrared Spectroscopic Study:
Naratriptan hydrochloride, excipients and their combination were analyzed by Infrared spectroscopy (FTIR 8400S) by KBr pellet method. They are compressed under high pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000 to 400 cm^{-1} in FTIR. The changes in the obtained peaks of pure drug excipients were compared with the drug-excipients mixture.

Evaluation of Post Compression Parameters:
Tablets were prepared using direct compression method all parameters were given in **(Table No. 3)** the **weights of tablets** were within ± 5% which falls within the acceptable weight variation ranges of ± 10%. **Hardness** of all formulations was in the range of 1.5-2 $Kg/cm.^2$ **Friability** values of the batches by addition of super disintegrants were found in the range of 0.48%-0.72%. Friability of batches by sublimation method was increasing when compared to direct compression batches (0.48%-0.72%), which is due to increase in porosity of the tablets. The results of friability indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling. **Thickness** of all formulations was between 2.31-2.42 mm indicating fairly acceptable tabulating. **Disintegration time** is very important parameter of ODT. The disintegration time of Formulation SF1-SF6 was satisfactory, because it disintegrates within 30 sec. The disintegration time of tablets of Formulation SF1-SF6 were found to be good because none of the tablet disintegrate greater than 15 sec. except one formulation SF3 (40 sec). Optimized final formula SF4 gives best disintegrating time i.e. 4-6 Sec. **Percentage drug content** (Assay) of Formulation SF1-SF6 was found to be between 99.1%-100.4%w/w. ***In vitro* dispersion time** was measured by the time taken to undergo uniform dispersion. The dispersion time of Formulations SF1 – SF11 was in the range of 6 -40 .In batches by sublimation method (SF1-SF6) except batch SF3 all the batches shown dispersion time between 6-11 sec were given in **(Table No.3)**. The rapid and uniform dispersion was observed in the Formulation SF4 due to presence of both disintegrants (Crospovidone, Croscarmellose sodium) and pore forming agent (Camphor). **Wetting time** of the formulation by sublimation technique (SF1 – SF6) was found in the range of 18-26 sec. on observation of all batches (SF1-SF6) wetting time of the tablets decreasing (18-22 sec) with increase in concentration of camphor which is due to the increase in the porosity of the tablet. **Water absorption ratio** is closely related to inner structure of tablets. The water absorption ratio values of Formulation SF1-SF6 were to found in the range of 53-68%.

RESULTS AND DISCUSSION:

The ODTs were prepared and the disintegration time was found 4-6 sec in Formulation SF4 which is in the acceptable limit as ideal ODT should disintegrate within a min. The ODTs of selected drug candidates passes the all quality control tests. On comparing all the formulation of batch SF1-SF6 sublimation method, shown higher friability due to the increase in porosity of the tablets after sublimation. In sublimation method porous structure is responsible for faster water uptake. Hence it facilitates wicking action of super disintegrants in bringing about faster disintegration. It is worthwhile to note that as concentration of camphor increases wetting time decrease. It can be concluded that Crospovidone (5%) and Croscarmellose sodium (4%) are better super disintegrants and Camphor (5%) better subliming agent for formulation of Orodispersible tablets of Naratriptan. In the finalized batches sublimation method (SF4), dissolution results shows more than 90%of the drug release within 10 minutes, which is significant in the bioavailability of water soluble drugs. It is confirming that the addition subliming agent is suitable for the preparation of Naratriptan ODT.

CONCLUSION:

In the present investigation we developed Orodispersible tablets of Naratriptan by using sublimation technique using camphor as sublimating agent. Sublimation technique using vacuum oven would be an effective alternative

approach in formulation of Orodispersible tablets. The dispersion pattern and disintegration of batch SF4 were found to be satisfactory. The total drug from the optimized batch was found to be released within the first ten minutes of dissolution study. The addition of super disintegrants method and sublimation method can be used to prepare ODTs of several categories of drug such as anti-emetics, antiallergic cardiovascular agents analgesic narcoleptics which need rapid onset of action. Faster disintegration of orally disintegrating tablets of above mentioned pharmacological categories improves the availability of drug for absorption in a faster rate. This may enhance the bioavailability. Faster disintegration and dissolution of Naratriptan ODT may give better therapy for the treatment of Migraine.

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LIST OF TABLES AND FIGURES

Table 1: Formulation Details of SF1-SF6

Ingredients	SF1	SF2	SF3	SF4	SF5	SF6
Naratriptan HCl	1.11	1.11	1.11	1.11	1.11	1.11
Mannitol	50	49	54	45	47.5	42.5
Lactose monohydrate	33.39	33.39	33.39	33.39	33.39	33.39
Camphor	5	5	5	5	2.5	7.5
Croscarmellose sodium	4	--	--	4	4	4
Crospovidone	--	5	--	5	5	5
Aspartame	3	3	3	3	3	3
Orange flavor	2	2	2	2	2	2
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Average weight	100	100	100	100	100	100

Table 2: Evaluation of Precompression Properties

Sr.No	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Bulk density (g/ml)	0.390	0.401	0.387	0.49	0.511	0.495	0.396	0.492	0.503
2	Tapped density (g/ml)	0.450	0.476	0.488	0.581	0.603	0.574	0.481	0.581	0.593
3	Compressibility Index (%)	13.3	15.7	15.5	14.43	15.04	13.76	19.11	14.21	13.98
4	Hausner's ratio	1.15	1.18	1.18	1.17	1.17	1.16	1.17	1.17	1.18
5	Angle of repose	26.7	29.4	28.7	27.1	28.3	27.9	30.0	26.2	28.1

Table 3: Results of Post Compression Properties of Naratriptan Tablets

Evaluation	SF1	SF2	SF3	SF4	SF5	SF6
Description	White	White	White	White	White	White
	Biconvex	Biconvex	Biconvex	Biconvex	Biconvex	Biconvex
	Circular	Circular	Circular	Circular	Circular	Circular
	Tablets	tablets	Tablets	Tablets	tablets	Tablets
Weight variation (mg)	100.1±0.3	102.1±0.2	103.5±0.3	103.4±0.2	102.6±0.1	103.3±0.2
Thickness (mm)	2.31-2.34	2.32-2.33	2.34-2.35	2.31-2.34	2.34-2.35	2.41-2.42
Friability (%)	0.62	0.64	0.48	0.50	0.48	0.72
Hardness(Kg/cm^2)	1.5-2	1.5-2	1.5-2.5	1.5-2.5	1.5-2.5	1.5-2.5
Disintegration time(sec)	4-6	3-4	30-35	4-6	5-7	4-6
Dispersion time(sec)	10-11	8-10	38-40	6-8	8-10	6-8
Water absorption ratio%	61-63	63-65	53-55	65-68	64-68	61-65
Assay(% w/w)	100.1	99.8	100.4	99.9	100.1	99.1
Wetting time(sec)	19-20	20-22	25-26	18-19	20-22	18-19

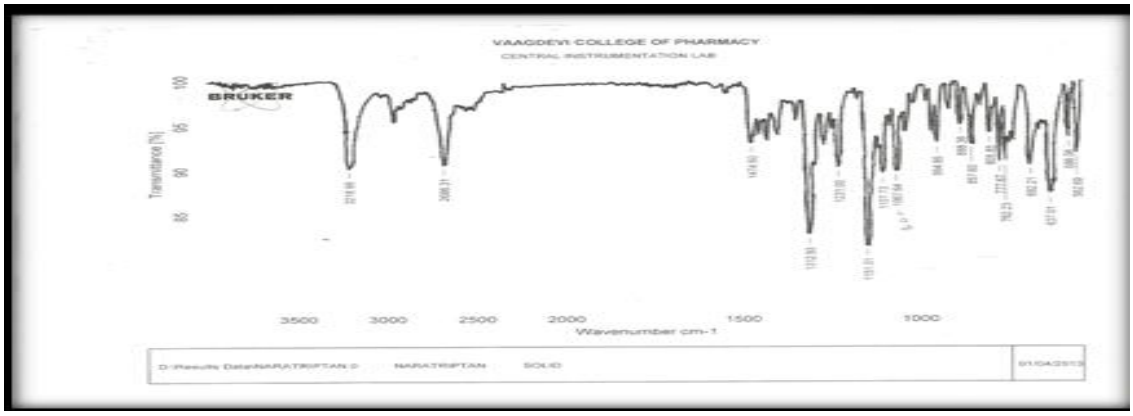

Fig 1: FTIR of Naratriptan

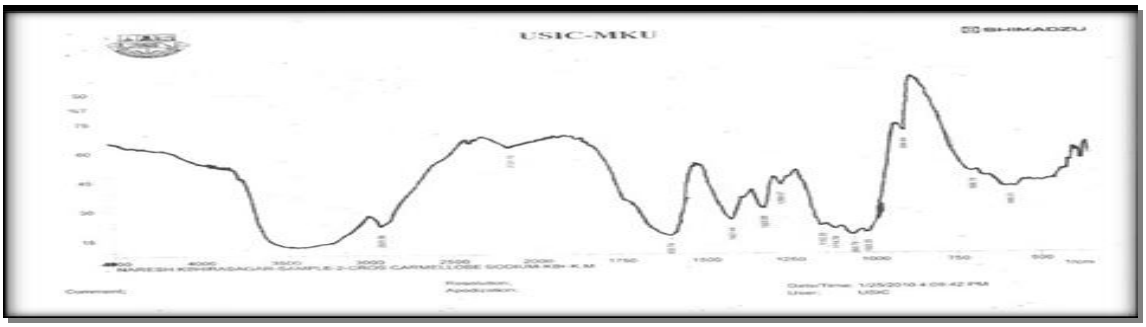

Fig 2: FTIR of Ac- Di-Sol

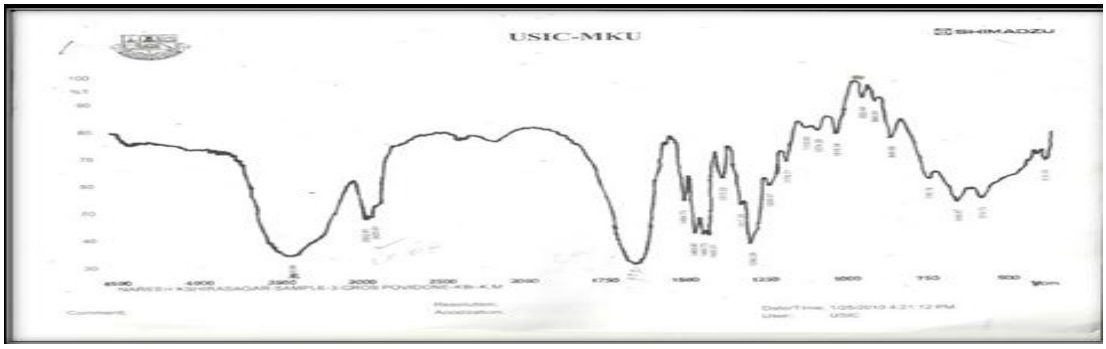

Fig 3: FTIR of Kollidon

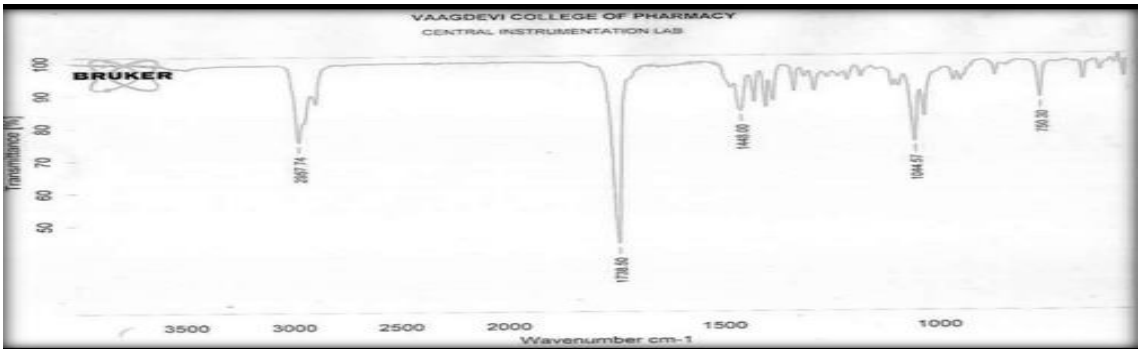

Fig 4: FTIR of Camphor

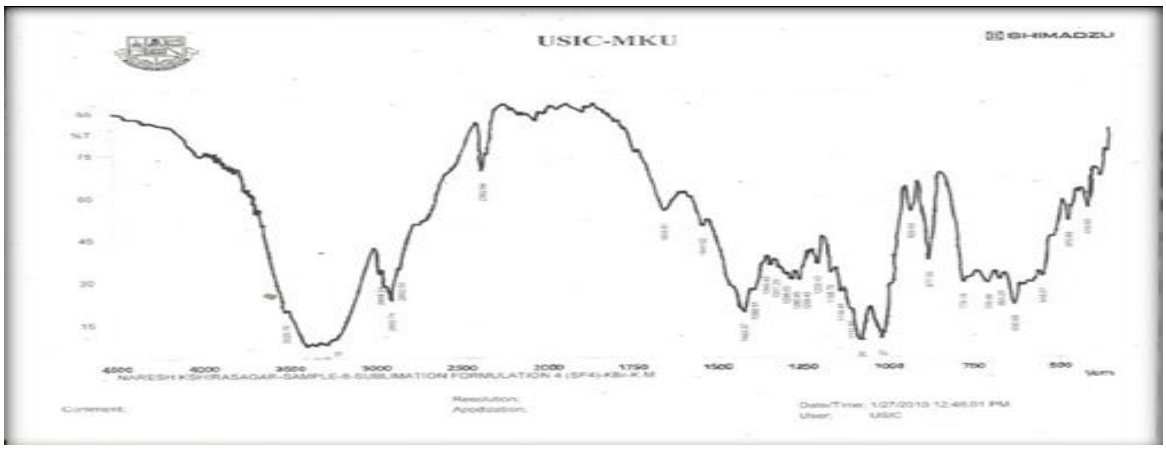

Fig 5: FTIR of Sublimation Formulation SF4

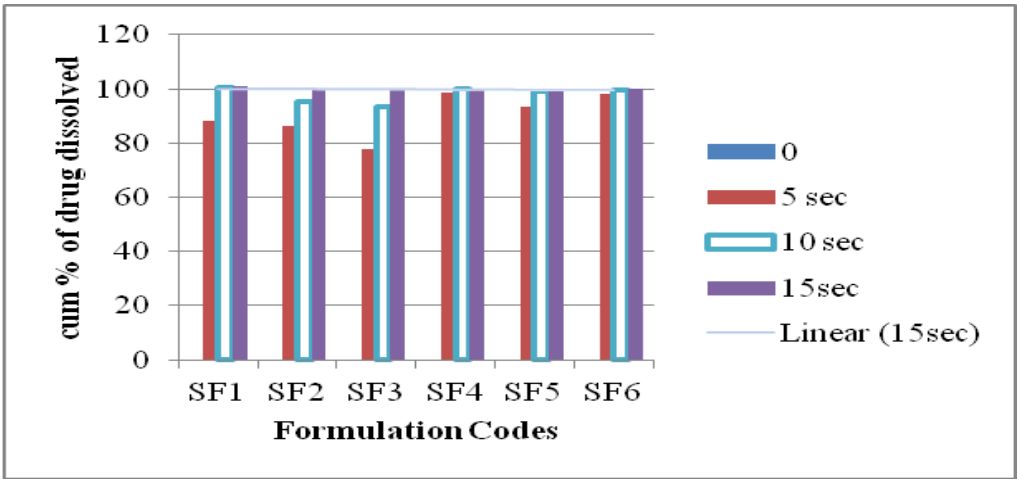

Fig 6: Comparative Study on Dissolution Profile of DC batch SF1-SF6