Formulation and Evaluation of Drotaverin Hydrochloride Liquisolid Compacts

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Abstract - In the present study, the potential of liquisolid compacts to improve dissolution properties of poorly water soluble agents was investigated using Drotaverine Hydrochloride. Drotaverine Hcl is an antispasmodic drug used orally for treatment. According to BCS, Drotaverine Hcl is a class II compound i.e, poorly water soluble .The Aim of present study was to improve the dissolution rate of Drotaverine Hcl using liquisolid compact technique .The techniques of liquisolid compacts is a promising method towards enhancing the dissolutions of poorly soluble drugs. Several formulations of liquisolid compacts having two different drug concentration were prepared. Cremophore EL, Micro crystalline cellulose pH 102 , Aerosil pH 200, cross carmellose sodium was used as a non-volatile liquid vehicle,carrier, coating material and super disintegrant respectively in all formulations. The prepared LS compacts powder blend were evaluated for their flow properties such as Bulk Density ,Tapped Density ,Angle of Repose ,Carr'scompressibility index and Hausner's ratio and the compressed liquisolid compacts are evaluated for the physical parameters such as Uniformity of weight , Hardness,Thickness. Friability, Disintegration,Content uniformity and Invitro dissolution .The FTIR and DSC analysis were performed to confirm the compatability of the drug with the excipients. Increase in Dissolution rate and Inturn improvement in bioavailability is observed in the case of poorly water soluble drug i.e,Drotaverine Hcl by this Liquisolid technique.

Key words: Drotaverine Hcl,Liquisolid compacts, Dissolution enhancement, Poorly soluble drugs, Fourier transformer infrared spectroscopy , Differential scanning calorimetery.

I. INTRODUCTION

The oral route of administration is the most prefered route of administration as it offers several advantages like ease of administration ,patient compliance, safe and effective. Solubility of the compound influences the drug absorption, bioavailability, pharmacokinetic profile. The 'Liquisolid compacts' technique is most commonly intended for the solubility enhancement, dissolution improvement and increases the bioavailability of drugs. Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities as well as for the generic development. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water solublecompounds. In this technique, a powdered form of liquid drug is formulated by converting liquid lipophilic drug or solution of water insoluble drug or drug suspension in suitable non-volatile solvents systems, in to dry looking, nonadherent, free flowing and readily compressible powdered mixtures by blending with the selected carrier and coating materials.[10] The good flow and compression properties of LS may be attributed due to large surface area of silica and fine particle size of avicel. Hence LS compacts containing water insoluble drugs expected to display enhanced dissolution characterisics and consequently improved oral bioavailability.[10]

In the present study LS compacts of poorly water insoluble drug Drotaverine hcl were formulated and evaluated by conducting precompression and post compression studies. The invitro dissolution studies of prepared LS compacts formulations was compared to those of conventionally prepared directly compressed tablets by using a USP-II apparatus. The FTIR and XRD studies are performed to conform any significant interaction between the drug and excipients used in the LS compacts.

II. CONCEPT

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Nonvolatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Fig. 1 shows lower contact angle of liquisolid compacts than the conventional tablets and thus improved wettability. [7]

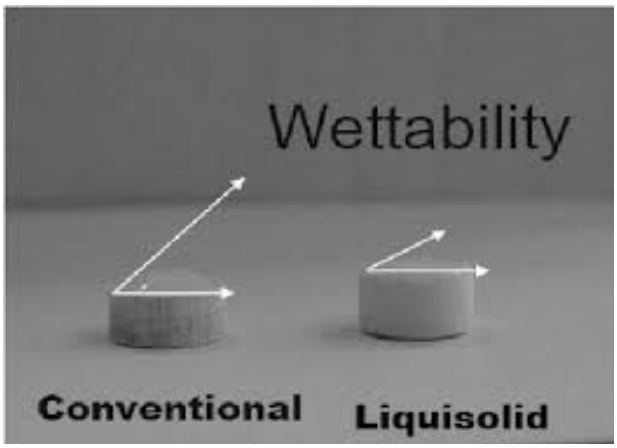

Fig. 1: Comparison of wettability between Conventional tablet and liquisolid compacts.

III. LITERATURE REVIEW WORK

Manish et al (2014) - The purpose of the present study is to develop a novel liquid solid technique which enhances the dissolution rate of water insoluble or poorly water soluble drugs of Nilvadipine, which belong to class II of BCS. Generally the liquisolid technique is based up on the admixture of drug loaded with non volatile solutions (or) liquid drug incorporated with required carrier and coating materials in order to obtain a dry, non adherent, free flowing and compressible powder. Various non volatile solvents used were Propylene glycol, Poly ethylene glycol. The solubility of drug in the non volatile solvents plays an important role in this formulation Avicel PH 102 and Aerosil were used as carrier and coating materials. Super disintegrants were used to increase the dissolution rate. Evaluation tests such as Disintegration time, Friability, Hardness and in-vitro dissolution studies were conducted. Amongst all the formulations F14 was considered to be the best in which Propylene glycol is used and the drug release was found to be 97% in 10 min.[6]

IV. METHODOLOGY

Solubility Studies :

For the selection of best non –volatile solvents solubility studies are carried out ,in this procedure, Pure drug was dissolved in different non-volatile solvents. Solubilty studies were carried out by adding or dissolving excess amount of pure drug to the different non-volatile solvents. From this obtained saturation solution were kept on the orbital shaker for 48hrs at 25^{o}C under constant vibration. After equilibrium, each test tube was centrifuged at 5000 rpm for 15minutes. Supernatant was filtered through membrane filter using 0.45µm filter disk. Filtered solution was appropriately diluted with 6.8 pH buffer media and UV absorbances were measured at 240nm wavelength. Concentration of dissolved drug was determined by using standard equation.[8]

Calculation of loading Factor (L_f):

Loading factors were calculated for carrier using solvent.

The "liquid load factor'' is termed as L_f (W/W) and is defined as the ratio of weight of the liquid formulation (W) over the amount or quantity of carrier material (Q) used in the system.

$L_f = W/Q$

The term "Carrier : Coating material Ratio" (R) refers to the ratio between the weights of the carrier (Q) and the coating material (q) used in the formulation.

$R=Q/q$

The liquid load factor that ensures acceptable flowability (L) can be determined by

$L_f = \phi + \phi. (1/R)$, where ϕ and ϕ are the ϕ values of the carrier and coating material respectively.[4,10]

Method of preparation of powder blend for liquisolid compact and conventional Tablets:

Conventional tablets of Drotaverine Hcl were prepared by direct compression using manual tabletting machine, each comprising of 20 mg drug with Microcrystalline cellulose ,Aerosil and cross carmellose sodium as excipients. Several Drotaverine Hcl liquisolid formulations were prepared at two different drug concentrations of 13.73% and 19.23%(w/w) in liquid vehicles. Each formulation containing microcrystalline as carrier , Aerosil as coating material, at carrier /coating ratio of 5,10,15,20,25&30. The appropriate amounts of carrier and coating materials used for each formulation based up on the L_f of that formulation. The drug – vehicle liquid system was prepared by mixing or titurating Drotaverine Hcl in non-volatile liquid vehicle using motar and pestle. Then a required or calculated quantities of carrier and coating materials were added to the above liquid medication under continuous stirring or mixing in a mortar with a pestle until the contents in the motar start of looking dry and are enough to maintain or attain acceptable flow and compression properties. To the above binary mixture super disintegrant like cross carmellose sodium is added and mixed for a period of 10 to 20 minutes in a motar. The final blend was compressed using the manual tabletting machine (Rimek,Karnavathi Engineering, India). To achieve required tablet hardness.[9,10]

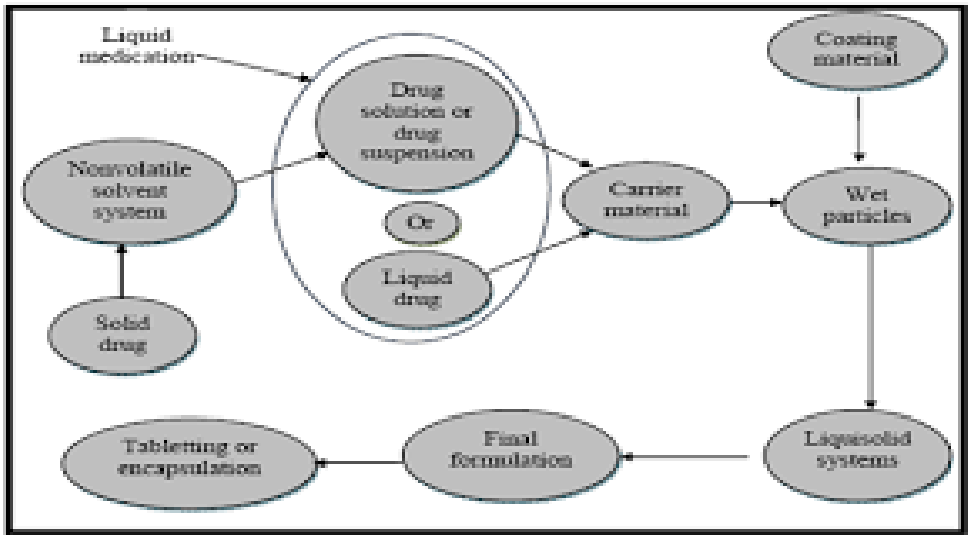

Fig. 2: Process involved in preparation of Liquisolid Compacts

Table no:1. Formulation chart of liquisolidcompactstable

S.no	Concentration of drotaverine inliqd.medication (%w/w)	Carrier: coating material R value	Loading factor	Microcryst Alline cellulose	Aerosil	Cross carmellose sodium	Unit in mg
F-1	13.73%	5	0.5914	280	56	20	521
F-2	13.73%	10	0.5810	285	28.5	19.16	498.26
F-3	13.73%	15	0.5710	290	19.3	18.92	493.82
F-4	13.73%	20	0.5257	300	15	19.2	499.2
F-5	13.73%	25	0.5136	310	12.4	19.52	507.52
F-6	13.73%	30	0.5009	320	10.6	19.8	516
F-7	19.23%	5	0.6458	320	64	25.28	657.28
F-8	19.23%	10	0.7402	335	33.5	24.66	641
F-9	19.23%	15	0.7045	330	22	24	624
F-10	19.23%	20	0.7157	330	16.5	23.78	618
F-11	19.23%	25	0.777	319	12.76	23.1	602.86
F-12	19.23%	30	0.7294	340	11.33	23.97	623.33

Compatability Studies Drug – excipient compatability studies like Fourier Transformer Infrared Spectroscopy and Differential scanning calorimeter studies (DSC) are carried out to determine if there is any significant changes or interactions between the drug and the excipient used in the liquisolid compact formulations.

Precompression studies of liquisolid powder blendAngle of repose(ɵ):The angle of repose of LS compact powder blend was determined by fixed height funnel method.Angle of repose of sample was calculated by using the following equation….(Θ) = $\tan^{-1}$ h/r

Where h and r are height and radius of powder cone [9]

Bulk density:It is the ratio of weight of the dry powder to its bulk volume, measured by formula

Bulk density (BD) = M /Vb

Where as m is the mass of powder and Vb is the bulk volume of the powder.[5]

Tapped density: It is the ratio of weight of the dry powder to its tapped volume, measured by formula

Tapped density (Td) =M / Vt

Where m is the mass of dry powder and Vt is the final tapped volume of powder.5

Compressibility index: percent carr's compressibility index of the prepared LS powder blend was calculated by using the formulaCarr'sindex(%) = [(Tapped density – Bulk density) x 100] / Tapped density 9

Hausner's ratio: was calculated from the following equation Hausner's ratio = Tapped density/Bulk density [9]

Post compression studies of liquisolid compacts

Weight variation test : 20 tablets were selected randomly from from each batch of formulations weighed individually each and both average weight and standard deviation of tablets were calculated.

Thickness: of the tablets was measured by Vernier callipers.20 tablets from batch were selected randomly and thickness was measured.

Hardness:hardness was tested for three tablets from each batch using Monsanto hardness tester.

Friability: Frability test was carried out by Roche friabilator apparatus. Six tablets were taken from each batch of formulation and rotated for 4minutes at 25 rpm. After revolutions the tablets were dusted and weighed again .

Disintegration time: disintegration test was carried by tablet disintegrator tester by selecting 6 tablets from each formulation. Distilled water at 37±2o C was used as disintegration media and time in minutes was recorded for each formulation after complete disintegration of tablet with no palable mass was remaining in the apparatus was measured.4

Drug content : Five tablets were powdered ,20mg equivalent weight of Drotaverine Hcl was weighed accurately and placed in volumetric flask. Then 10ml of methanol was added and sonicated for 10mins after vigorous shaking and the volume was made up to 100ml with 6.8pH phosphate buffer. Followed by fitration ,dilution of the resulting solution and analysed spectrophotometrically at 240nm using UV-visible double –beam spectrophotometer.9,5

Invitro dissolution test:The invitro drug release study of tablet was performed by using USP type –II apparatus(paddle method) .The dissolutiontest was performed using 900ml of 6.8pH phosphate buffer as dissolution media at 37±0.5oC maintained at 100rpm. At the predetermined time intervals, 5ml of sample was withdrawn and replaced with the 5ml of fresh dissolution media. The withdrawn test samples were filtered through a 0.45 µm membrane filtered& diluted when necessary using Shimadazu UV-visible doublebeamspectrophotometer at λmax 240nm.

V. RESULTS AND DISCUSSION

1.Preparation of caliberation curve of Drotaverine hcl in 6.8pH phosphate buffer

Table No: 2 .Caliberation Data Of Drotaverine Hcl In6.8 Ph Phosphate Buffer

S.no	Concentration (µg/ml)	Absorbance at
1	0	0
2	0.2	0.1201
3	0.4	0.2364
4	0.6	0.3364
5	0.8	0.463
6	1	0.589
7	1.2	0.6345
8	1.4	0.7444
9	1.6	0.8862
10	1.8	0.9661

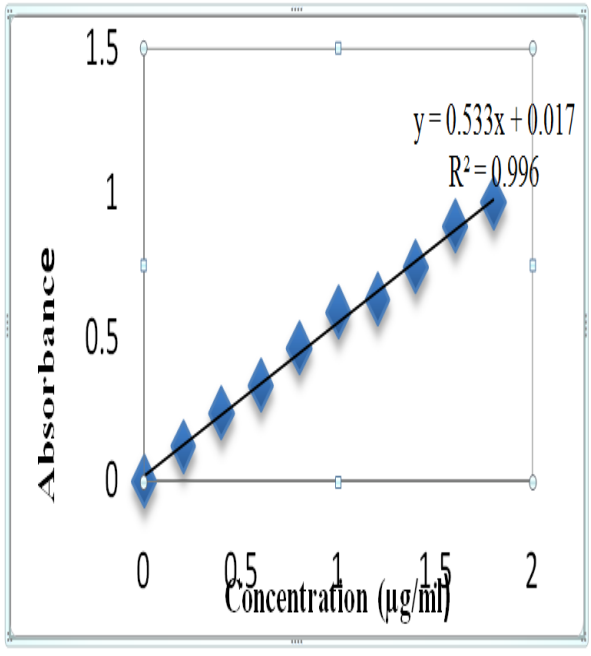

Fig.no:3.Standardgraph of drotaverinehcl in 6.8pH Phosphatebuffer

2.Solubility studies

Table.No:3.Solubility Studies Of Drotaverine Hcl In Various Nonvolatile Solvents

S.no	Non-volatile solvents	Concentration(mg/ml)
1	Tween-20	0.08
2	Tween-80	0.6303
3	Span-20	0.132
4	Polysorbate -80	0.032
5	Castor oil	0.0029
6	Glycerine	0.1513
7	PEG-200	2.084
8	PEG-400	0.1162
9	PEG-600	0.079
10	Propylene glycol	0.1671
11	Acrysol EL-135	104.5
12	PEG-300	3.53
13	Water	8.063
14	Cotton oil	1.74
15	Olive oil	0.0113
16	Sesame oil	8.45

3.Drug –Excipient Compatability studies

A)Fourier Transformer Infared Spectroscopy

From the spectra of drotaverine, combination of drotaverine with excipients. It was observed that characteristic peaks of drotaverine were present in the combination spectra. Thus indicating the compatability of drotaverine and excipient .IR Spectra are shown below[8]

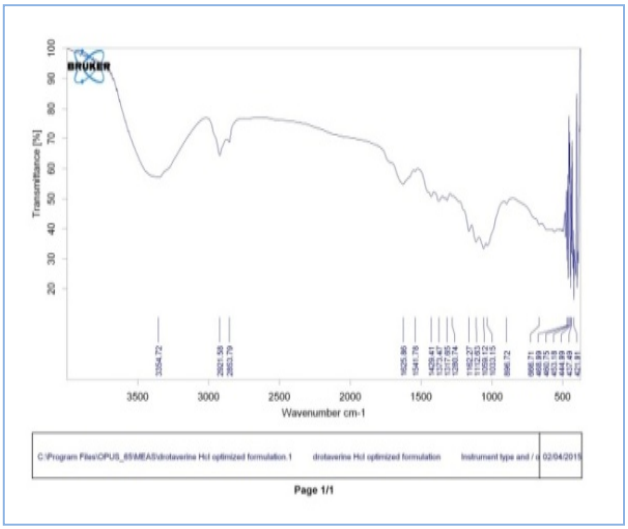

Fig .no: 4 .IR Spectra of Drotaverine hcl formulation

Table.No:4.Ftir Spectra Studies Of Drotaverine Hcl And Optimized Lscompact Formulation

S.no	Data interpretation		Nature of bond	Type of Functional group
	Wave number in formulation	Characteristic wave number range (cm^{-1})		
1	3354.72	3478.33	O-H Stretch, H-bonded	Alcohols, phenols
2	2921.58	2980.15	O-H stretch, C-H strecth	Carboxylic acids,Alkanes
3	1625.86	1603.57	N-H bend	Primary amine
4	1541.78	1517.93	N-O asymmetric stretch	Nitro compounds
5	1429.41	1431.38	C-C Strecth	Aromatics
6	1280.74	1281.65	C-O strecth, C-N stretch, C-H wag	Alcohols,carboxylic acids,esters,ethers. Aromatic amines Alkyl halides
7	896.72	894.8	C-H ‘oop’ N-H wag	Aromatic, Primary and secondary amines

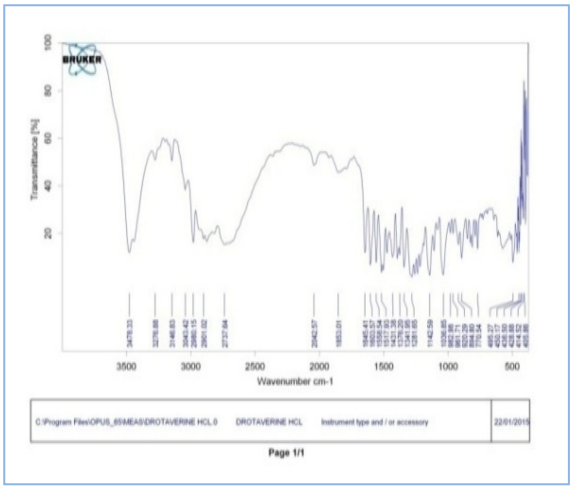

Fig.no:5 IR Spectra of optimized liquisolid compact

B) Differential Scanning Calorimetery

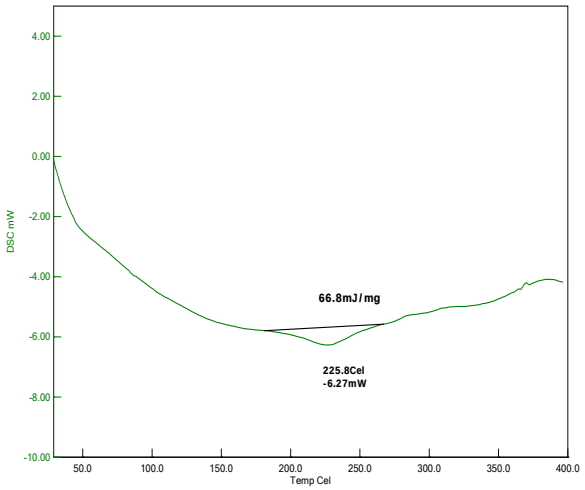

Fig.no:6.DSC of Pure Drug Drotaverine hcl formulation

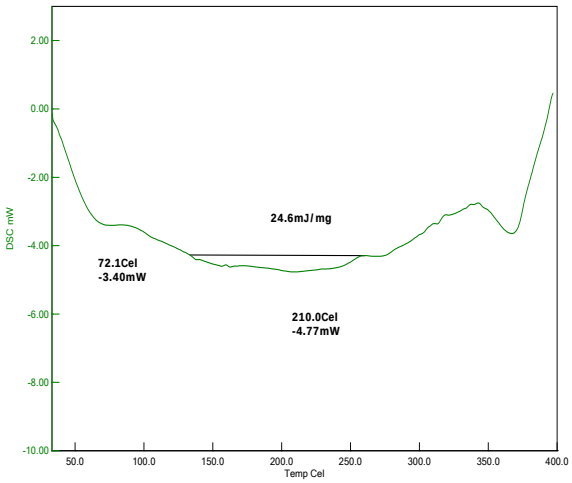

Fig.no:7.DSCof optimizedLScompact

The drug Drotaverine showed a sharp endothermic peak at 225oC indicating the crystalline nature of drug. DSC thermograms of liquisolid formulations showed a characteristic peak at 210oC as shown in fig.no:6 and 7.As the decrease in area and sharpness of characteristic endothermic peak of drug which indicates conversion of most of the crystalline form of the drug to the amorphous form.4

4.Precompression Evaluation Parameters

Flow properties of liquisolid compacts blend which were evaluated for angle of repose, bulk density,tapped density, carrs index and Hausners ratio were given as below

Table.No:5.Results Of Precompression Flowproperties Of Liquisolid Compact Powder Blend

Formuln no	Angle of repose (%)	Bulkdensity (g/cm^3)	Tapped density (g/cm^3)	Carrs index(%)	Hausners ratio
F-1	30.52	0.16	0.19	21	1.18
F-2	29.05	0.14	0.17	17.6	1.21
F-3	32.79	0.15	0.19	21	1.26
F-4	29.74	0.15	0.17	11.76	1.13
F-5	29.28	0.15	0.18	16	1.2
F-6	27.69	0.14	0.17	17.6	1.21
F-7	33.06	0.17	0.19	10.52	1.11
F-8	26.05	0.18	0.2	10	1.11
F-9	37.77	0.17	0.21	19	1.23
F-10	33.33	0.19	0.22	13.6	1.15
F-11	27.51	0.17	0.21	19	1.23
F-12	30.52	0.18	0.23	21.7	1.27

5.Post compression Evaluation Parameters

Weight variation test: From all the twenty tablets,the entire tablets passed weight variation test as the percentage weight variation test and was found to be with in the pharmacopeia limits (i.e,5%)

Thickness: the thickness of formulation F-2 was found to be lowest where as F-7 was of highest thickness as shown in table no.6

Hardness: the hardness of LS compacts tablets depends on the amount of carrier and coating materials used in the formulations.It was found to be 3.74 to 4.71kg/cm2 as shown in table no:6

Friability: Frability of the all the formulations were found to be with in the limits ranging from 0.2 -0.9% as shown in table no:6.

Disintegration time: Disinintegration time of all the LS Compacts tablets was found to be ranging from 2min13sec to 3min92sec as shown in table no .6.

Drug content : the percentage drug content was varying from 94.12 to 98.76% as shown in table no:6.

Dissolutiontest: The invitro drug release profiles of liquisolid compact tablets and conventional tablets of drotaverine hcl is shown in fig.no:8&9. From the dissolution profiles,it is observed that all liquisolid formulations significantly improved drug dissolution compared to conventional drug conventional tablets. Due to the significant increase in the wetting properties and surface area of the drug particles available for dissolution as the liquisolid tablets were excepted to enhance the drug release and consequently improved oral bioavailability.

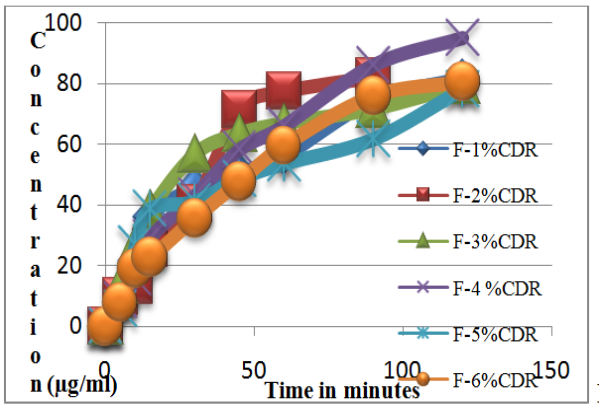

Fig.no:8.Drug release profiles of formulations F-1 to F-6.

Table No:6.Results Of Post Compression Parameters Of Liquisolid Compact Tablets

Formuln. no	Weight variation test	Thickness (mm)	Hardness (kg/cm^3)	Friability (%)	Disintegration time	Drug content (%w/w)
F-1	Compiles	4.05	4.09	0.6	2min 13 sec	94.12
F-2	Compiles	3.8	4.01	0.7	3min 92sec	98.58
F-3	Compiles	3.81	3.74	0.3	3min 71sec	96.46
F-4	Compiles	3.84	4.11	0.6	3min 64 sec	98.76
F-5	Compiles	4.18	4	0.9	2min 49sec	97.74
F-6	Compiles	4.27	4.12	0.6	3min 05sec	94.37
F-7	Compiles	4.87	4.71	0.7	2min 82 sec	97.27
F-8	Compiles	4.48	4.47	0.7	3min 3sec	96.03
F-9	Compiles	4.45	4.21	0.8	3min 12sec	97.64
F-10	Compiles	4.27	4.19	0.2	3min 09esc	94.1
F-11	Compiles	4.51	4.17	0.5	3min 24sec	95.52
F-12	Compiles	4.52	4.24	0.8	3min 27sec	95.33

Table.No:7.Invitro Drug Release Data Studies Of Drotaverinehcl Ls Compacts Formulation

Time in mins	F-1 %CD	F-2 %CD	F-3 %CD	F-4 %CD	F-5 %CD	F-6 %CD	F-7 %CD	F-8 %CD	F-9 %CD	F-10 %CD	F-11 %CD	F-12 %CD
0	0	0	0	0	0	0	0	0	0	0	0	0
5	7.4	9.72	14	8.9	5.8	7.86	5.3	10.8	9.2	14.33	6.98	12.8
10	15.08	13.6	26.94	15.9	26.9	18.97	14.5	16.5	25.61	22.24	22.96	26.13
15	36	25.8	38.29	29	38.71	22.58	21.91	36.13	34.78	46.13	38.21	35.56
30	45.59	40.46	56.71	43	41.14	35.61	29.44	40.1	38.47	50.23	46.68	40.1
45	50.56	71.32	63.37	58.2	48.6	47.64	40.7	45.5	46.1	63.21	62.09	55
60	56	77.4	66.81	66	53.63	59.46	53.52	61.21	51.71	71.04	66.95	6.5
90	74.3	82.11	71.46	86	61.65	75.79	78.24	70.53	69.9	74.54	75.22	69.23
120	81.49		79.31	94.97	78.07	80.42			79.82			77.7

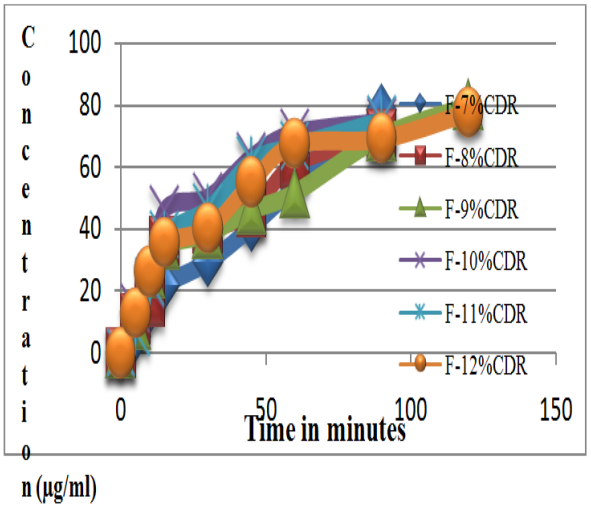

Fig.no:9.Drug release profiles of formulations F-7 to F-1

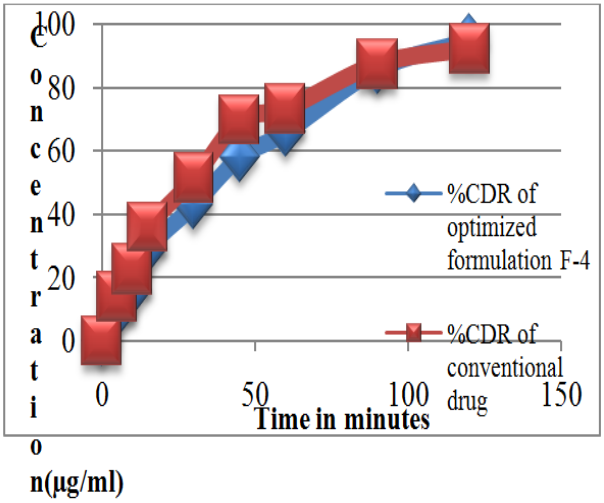

Fig.no:10.Invitro drug belease profile of optimized LS compacts F-4 with marketed product

Table.No:8.Comparision Of Invitro Drug Release Data Studies Of Optimized Formulation F-4 With Conventional Tablet

Time in mins	%CDR of optimized formulation	%CDR of conventional drug
0	0	0
5	8.9	13.83
10	15.9	22.61
15	29	35.79
30	43	51.33
45	58.2	69.78
60	66	73.25
90	86	87.36
120	94.97	92.21

VI. CONCLUSION

The aim of the study was to increase the dissolution profile their by increasing solubility. Solubility is the major criteria to achieve desired concentration of the drug in the systemic circulation. About 80% of drugs are poorly soluble in nature .So in order to overcome this problem ,Several techniques has been developed to enhance the solubility of those poorly soluble drugs.Among them Liquisolid compacts is the most promising and new technique which promotes the dissolution rate of water insoluble drugs.Hence in this study liquisolid compacts was chosen to enhance the dissolution rate of Drotaverine Hcl .Drotaverine Hcl LS compacts tablets were prepared by using Acrysol EL-135/Cremophore EL ,Microcrystalline cellulose, Aerosil ,cross carmellose sodium as non-volatile solvent, carrier, coating material, and super disintegrant respectively .From all LS compacts formulations,F-4 was found to be optimized formulation as it shown desired drug release along with acceptable physical properties. 8.

VII. FUTURE SCOPES OF THE STUDY

By studying all the above factors which are mentioned , it is proposed that as this method is simple, precise, accurate ,cost effective and can be used to manufacture liquisolid compacts of Drotaverine Hcl as Pharmaceutical Oral Dosage Form for relieving spasm of smooth muscles in visceral organs, chronic gastric and deudonal ulcers, head ache associated with cerebra vasospasm and spasm of periphery artery in patients for immediate action.

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