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Bioavailability Enhancement of Furosemide by Hydrotropic Solid Dispersion Technique

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Abstract Bioavailability Enhancement of Furosemide by Hydrotropic Solid Dispersion Technique. In the current study, Bioavailability Enhancement of Furosemide by Hydrotropic Solid Dispersion Technique were performed. Preformulation study, various physical parameters i.e. solubility, bulk density, tapped density, angle of repose etc were studied. Along with these studies, SEM and TEM were also studied. Initially solubility of furosemide was determined individually in 4 hydrotropic agents namely urea (U), sodium acetate (A), sodium benzoate (B), sodium citrate (C) at concentration of 10%, 20%, 30% and 40% solutions. The X.R.D. pattern of furosemide shows intense and sharp peaks that prove crystalline nature of furosemide. Also X.R.D. patterns of solid dispersion and physical mixture gave sharp and intense peaks and are thus easily comparable with that of furosemide. The diffraction pattern of solid dispersion and physical mixture showed some peaks at 2Ɵ of 18.0, 18.9, 27.7 and 28.6 which are characteristic of pure furosemide. Floating dosage forms can significantly prolong the gastric residence time of drugs and thus can improve bioavailability, reduces drug waste with new therapeutic possibilities and substantial benefit to the patients.

Keywords Floating dosage forms, Solid dispersion, Bioavailability Enhancement, Furosemide, Hydrotropic Technique

1. Introduction

The solid dispersion has become an established solubilization technology for poorly water-soluble drugs. Since a solid dispersion is basically a drug–polymer two-component system, the drug–polymer interaction is the determining factor in its design and performance. Solid Dispersion technology has been specially developed to provide two different release rates or dual release of a drug from a single dosage form[1]. The tablets are prepared by two separate direct compression steps that combine an immediate release layer for rapid onset of action and a controlled release matrix complex within a tablet for prolonged release. [2,3] The prolonged release matrix remains intact and slowly absorbs fluid from gastro intestinal tract, which cause the matrix to expand and transforms the polymer into a porous, viscous gel that serves as a barrier between the drug and surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.[4,5]

The objective of the current work was to develop such an oral dosage form which can provide immediate release of orally administered Furosemide so that fast onset of diuretic action can be achieved within few minutes and thus

parental therapy of Furosemide can be replaced by oral therapy and at the same time retaining the advantage of parental therapy. [6]

2. Materials and Methods

Drug Identification Tests as per I.P 1996

U.V. Absorption [7]

The light absorption in the range 220 to 360 nm of a 0.0005% w/v (5 µg/ml) solution in 0.1 M sodium hydroxide was determined and the ratio of the absorbance at the maximum at about 271 nm to that at the maximum at about 228 nm was noted.

Melting Point Test [7]

The melting point of furosemide was determined using open capillary method.

Preparation of Calibration Curve of Furosemide [7]

Accurately weighed 50 mg of furosemide was dissolved in 900 ml of D.M. water in a 1000 ml volumetric flask and then volume was made up to 1000 ml with D.M. water. Appropriate dilutions were made with D.M. water so as to obtain a series of solutions in concentration range of 10 – 50 µg/ml. The absorbances of dilutions were measured on Shimadzu U.V. – 1700 A double beam spectrophotometer at λ_{max} of 333 nm against respective reagent blanks. This procedure was done in triplicate and the average was calculated.

Solubility of Furosemide [7]

Accurately measured 5 ml of D.M. water was taken in a volumetric flask and excess amount of drug was added and shaken for 12 hr in Orbital Flask Shaker (Khera instruments Pvt. Ltd., India). The solution was allowed to equilibrate for 24 hrs. Then, solution was centrifuged at 2000 r.p.m. for 5 minutes in ultra-centrifuge and was filtered through Whatman grade 41 filter. Aliquot was suitably diluted and analyzed using UV spectrophotometer at 333 nm. Same procedure was repeated with 0.1N HCl to determine the solubility of furosemide in 0.1N HCl.

Furosemide Hydrotropic Agent Interference Study

For determination of interference of hydrotropic agents in the spectrophotometric estimation of furosemide, the absorbances of the standard solutions of furosemide were determined in D.M. water alone and in the presence of the hydrotropic blend employed for formulation purpose. The absorbances were recorded against respective reagent blanks at appropriate wavelengths and results are shown. A uv-visible recording spectrophotometer (Shimadzu, U.V. 1700 A Japan) with 1 cm matched silica cells was employed for spectrophotometric determinations.

Approximate Solubility Determination in Different Blends of Hydrotropic Agents

Initially, weight of a 10 ml volumetric flask filled with 3 ml of a particular blend of hydrotropic solution was determined. Then small aliquot of drug was added and flask was shaken manually so as to dissolve the drug. When drug got solubilized, further small aliquots were added and procedure was repeated till hydrotropic solution got nearly saturated. Then, weight of volumetric flask with saturated solution was determined. Finally, the difference in weight gave the approximate amount of drug dissolved in 3 ml of hydrotropic solution, from which the approximate percentage of drug solubilized was calculated.

Equilibrium Solubility Studies in Different Blends of Hydrotropic Agents [8]

Accurately measured 3 ml of a particular blend of hydrotropic agent was taken in a 10 ml volumetric flask and excess amount of drug was added and mechanically shaken until saturated solution was formed. Then solution was centrifuged at 2000 r.p.m. for 5 minutes in ultra-centrifuge and then solution was filtered through Whatman grade 41 filter. Aliquot was suitably diluted with D.M. water and analyzed using UV spectrophotometer at 333 nm.

Formulation of Hydrotropic Solid Dispersions of Furosemide [8]

For preparation of hydrotropic solid dispersion in 1:6 ratio, accurately weighed 2.25 gm urea, 3 gm of sodium benzoate, 0.75 gm of sodium citrate (so that total weight of the mixture was 7 gm) were taken in a 100 ml beaker and were mixed properly. Then, minimum possible quantity of warm, demineralized water sufficient to dissolve the above mixture was added, because lesser the amount of water lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely (during removal of water).

Dissolution of the hydrotropic mixture was facilitated by agitation of a Teflon coated magnetic rice bead on a high speed magnetic stirrer. After complete dissolution of hydrotropic mixture, 1 gm of furosemide was dissolved in the above solution and temperature was maintained in the range of 55- 60ºC so as to facilitate the evaporation of water.

Formulation of Physical Mixture of Furosemide [8]

For preparing physical mixture in 1:6 ratio, accurately weighed 1gm of furosemide, 2.25 gm of urea, 3 gm sodium benzoate and 0.75 gm of sodium citrate were mixed using geometric dilution technique and were intensely triturated using glass pestle mortar. After complete mixing, the powder mass was passed through sieve # 60 and was finally stored in an air tight glass bottle. Same procedure was utilized to prepare physical mixture in the ratio of 1:8, 1:10, and 1:12 using appropriate quantity of hydrotrope.

Dissolution Rate Studies [8]

Solid dispersion or physical mixture equivalent to 20 mg of Furosemide were tested in dissolution rate studies using U.S.P. XXIV (type II) dissolution test apparatus (Model TDT6P, Electro lab Mumbai, India) with paddle to rotate at 50 r.p.m. 900 ml of 0.1 N HCl was taken as dissolution media with temperature of 37$\pm$ 0.5°C. At definite time interval 10 ml of the sample were withdrawn and were analyzed for drug content. Withdrawn samples were also replaced with fresh dissolution media.

Micromeritic Properties of Solid Dispersions [9]

Any method of measuring powder flow must be practical, useful, reproducible and sensitive, and must yield meaningful results, but actually no simple powder flow method is adequate or complete to characterize the wide range of flow properties experienced in the pharmaceutical industries.

Bulk Density

Accurately weighed, 5 gm of solid dispersion were filled in a 10 ml graduated cylinder and its unsettled volume, Vo was noted. The bulk density was calculated in gm/cm^3 by the following formula.

$$\textbf{Bulk density } (D_o) = M/V_o$$

where, M = Mass of powder taken, V_o= Apparent volume.

Tapped Density [9]

Accurately weighed, 5 gm of solid dispersions were filled in a 10 ml graduated cylinder. The tapping of the cylinder was done on a wooden surface for 500 times and the tapped volume V_i was noted. Tapping was continued further for additional 750 times and the tapped volume, V_f was noted. The difference between two tapping volume was less than 2%, so V_f was considered as a tapped volume. The tapped density was calculated in gm/ cm^3 by following formula.

$$\textbf{Tapped density } (D_f) = M/V_f$$

Where, M = weight of sample powder taken, V_f = Final tapped volume

Compressibility index and Hausner ratio [10]

For a poorly flowing powder there are frequently greater inter-particulate interactions and therefore a greater difference in the bulk density and tapped density. These differences are also reflected in the Carr's index and Hausner ratio.

Angle of repose [10]

Approximately 25 g of granulation blend was transferred through the funnel. The height of the pile (h) and the radius of the base (r) were measured with the ruler. The angle of repose was calculated using the formula mentioned.

$$\tan \theta = h/r \quad \text{or} \quad \theta = \tan^{-} h/r$$

Powder X-Ray Diffraction Studies

Random orientation of a crystal lattice in a powder sample causes the X-ray to scatter in a reproducible pattern of peak intensities at distinct angles (θ) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. An amorphous form does not produce a pattern. [9]

The sample was spread on a graticule and pressed in such a way that sample did not fall on keeping the graticule vertical. The graticule was placed in sample holder and exposed to C_uK_α-radiation (40 KV, 50 MA), $2\theta = 5^o$ to 40^o at a scanning speed 4^0/min and step size 0.02^o 2θ.

Differential Scanning Calorimetric Studies

Differential scanning calorimetry (DSC) and differential thermal analysis (DTA) measure the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. Examples of endothermic (heat-absorbing) processes are fusion, boiling, sublimation, vaporization, desolation, solid-solid transitions and chemical degradation. Crystallization and degradation are usually exothermic processes. Quantitative measurements of these processes have many applications in Preformulating studies including purity, polymorphism, salvation, degradation and excipient compatibility. [9]

Scanning Electron Microscopy

The scanning electron microscopy is a type of electron microscopy that images the sample surface by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition and other properties such as electrical conductivity. [9]

Result & Discussion

U.V. Absorption

Table 1: UV absorbance's of Furosemide

S. No.	Absorbance			Ratio of Absorbance
	228 nm	271 nm	333 nm	
1.	0.555	0.312	0.064	0.562
2.	0.554	0.314	0.060	0.567
3.	0554	0.314	0.060	0.567

Melting Point Test

The average of three values was considered as the melting point of drug.

Table 2: Melting point determination

S. No	Melting Point (ºC)	Average
1	208.0	207.3
2	207.6	
3	206.4	

Preparation of Calibration Curve of Furosemide

The absorbance data obtained are shown in Table 3.

Table 3: Absorbance data for calibration curve of furosemide in D.M. water

S. No	Concentration (µg/ml)	Absorbance (333nm)
1	10	0.148
2	20	0.297
3	30	0.439
4	40	0.591
5	50	0.748

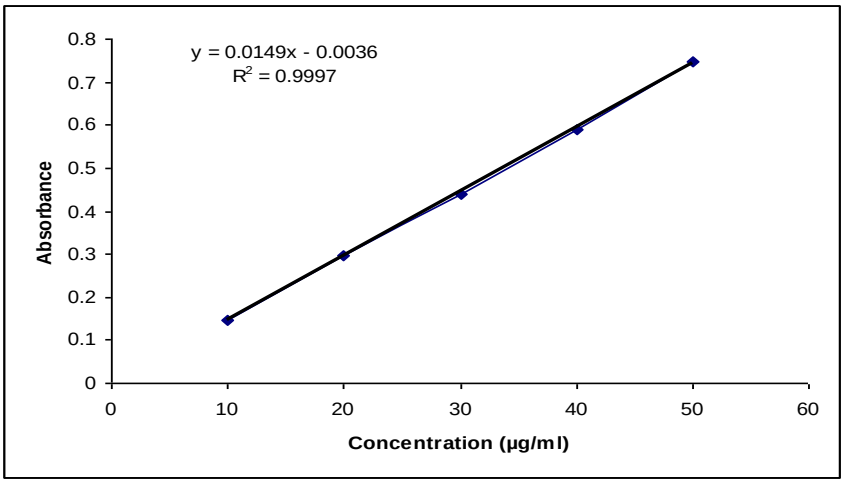

Fig. 1: Calibration curve of furosemide in demineralized water

Accurately weighed 50 mg of furosemide was dissolved in 900 ml of 0.1 N HCl in a 1000 ml volumetric flask and then volume was made upto 1000 ml with 0.1 N HCl. Appropriate dilutions were made with 0.1 N HCl so as to obtain a series of solutions in concentration range of 10 – 50 µg/ml. The absorbances of dilutions were measured on Shimadzu U.V. – 1700 A double beam spectrophotometer at λ_{max} of 333 nm against respective reagent blanks. This procedure was done in triplicate and the average was calculated. The absorbance data obtained are shown in Table 4.

Table 4: Absorbance data for calibration curve of furosemide in 0.1 N HCl

S. No	Concentration (µg/ml)	Absorbance (333nm)
1	10	0.154
2	20	0.309
3	30	0.471
4	40	0.612
5	50	0.749

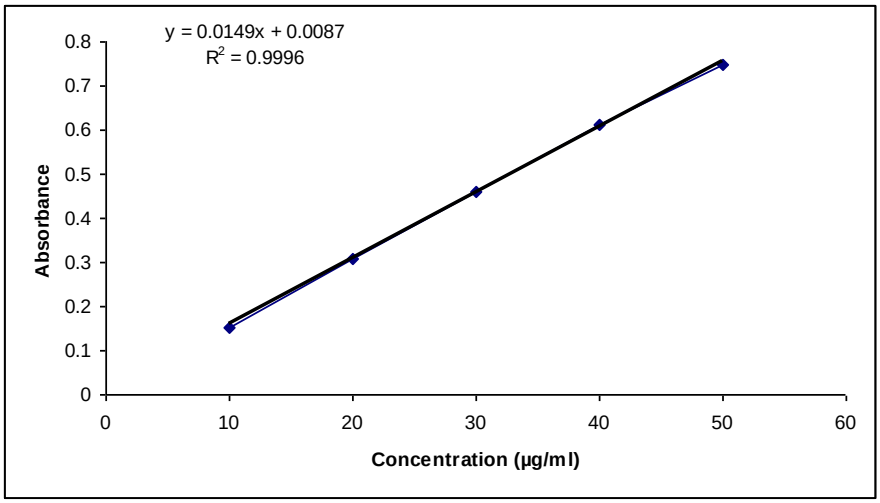

Fig. 2: Calibration curve of furosemide in 0.1N HCl

Accurately weighed 50 mg of furosemide was dissolved in 900 ml of different hydrotropic solutions in a 1000 ml volumetric flask and then volume was made upto 1000 ml with 0.1 N HCl. Appropriate dilutions were made with different hydrotropic solutions so as to obtain a series of solutions in concentration range of 10 – 50 µg/ml. The absorbances of dilutions were measured on Shimadzu U.V. – 1700 A double beam spectrophotometer at λ_{max} of 333

nm against respective reagent blanks. This procedure was done in triplicate and the average was calculated. The absorbance data obtained are shown in Table 5 for the estimation of furosemide in respective blends of hydrotropic solutions.

Table 5: Regression equations of furosemide in different hydrotrope blends

S. No	Hydrotrope in D.M. water	Regression equation	R^2
1	U	Y=0.0149X+0.0122	0.9950
2	A	Y=0.0151X+0.0173	0.9940
3	C	Y=0.0151X+0.0103	0.9992
4	B	Y=0.0145X+0.0227	0.9984
5	U+A	Y=0.0147X+0.0206	0.9987
6	U+B	Y=0.0157X+0.0064	0.9977
7	U+C	Y=0.0145X+0.0315	0.9955
8	A+B	Y=0.0143X+0.0250	0.9979
9	A+C	Y=0.0147X+0.0162	0.9982
10	B+C	Y=0.0152X+0.005	0.9997
11	U+A+B	Y=0.0149X+0.0102	0.9993
12	U+A+C	Y=0.0153X+0.0061	0.9981
13	A+B+C	Y=0.0147X+0.0171	0.9902
14	U+B+C	Y=0.0149X+0.0086	0.9955
15	U+A+B+C	Y=0.0151X+0.0090	0.9970

Where, U= urea, A= sodium acetate, B = sodium benzoate, C = sodium citrate

SOLUBILITY OF FUROSEMIDE

Results are shown in Table 6.

Table 6: Furosemide solubility

S. No.	Solvent	Solubility of furosemide (µg/ml)
1	D.M. water	82
2	0.1 N HCl	67

FUROSEMIDE HYDROTROPIC AGENT INTERFERENCE STUDY

Table 7: Drug-hydrotrope interference study

Drug	Solvent system used	Drug conc. (µg/ml)	Hydrotrope conc. (µg/ml)	Wave length (nm)	Absorbance against resp. blank
Furosemide	D.M. Water + S.A	20	1000	333	0.301
Furosemide	D.M. Water + S.B	20	1000	333	0.306
Furosemide	D.M. Water +S.C	20	1000	333	0.300
Furosemide	D.M. Water + Urea	20	1000	333	0.303
Furosemide	D.M. Water	20	1000	333	0.301

EQUILIBRIUM SOLUBILITY STUDIES IN DIFFERENT BLENDS OF HYDROTROPIC AGENTS

Initially solubility of furosemide was determined individually in 4 hydrotropic agents namely urea (U), sodium acetate (A), sodium benzoate (B), sodium citrate (C) at concentration of 10%, 20%, 30% and 40% solutions.

From the results of above studies it was concluded that solubility of furosemide was increasing with increasing concentrations of hydrotropic agents, for example solubility in 40 % urea solution was found to be much higher than solubility in 10%, 20% or 30% urea solutions.

Table 8: Equilibrium solubility of furosemide in different hydrotropic blends

S. No.	Hydrotropic Agents	Concentration (w/v)				Solubility enhancement ratio
		10%	20%	30%	40%	
1	Urea	0.067	0.094	0.131	0.191	23.875
2	Sodium Acetate	0.013	0.078	0.142	0.239	29.857
3	Sodium Benzoate	0.283	0.627	1.171	2.157	296.632
4	Sodium Citrate	0.015	0.034	0.060	0.129	16.125

Highest solubility was obtained in 40% sodium benzoate solution. Then, in order to decrease the concentration of sodium benzoate, different combinations of above mentioned 4 hydrotropic agents in different ratios were tried to determine enhancement in solubility, so that total concentration of hydrotropic agents was always 40% w/v. So, all possible combinations of 2 hydrotropic agents were taken in such a way that total concentration was always 40% with fixed ratio of 20:20. As shown in Table 9.

Table 9: Equilibrium solubility of furosemide in different hydrotropic blends

S. No.	Combination	Total Conc. (%w/v)	Individual conc. (%w/v)	Solubility (%w/v)	Solubility enhancement ratio
1	U + A	40.00	20.00	0.651	81.375
2	U + B	40.00	20.00	2.909	363.625
3	U + C	40.00	20.00	0.943	117.875
4	A + B	40.00	20.00	2.148	268.516
5	A + C	40.00	20.00	0.067	8.375
6	B + C	40.00	20.00	3.005	375.625

Where, U= urea, A= sodium acetate, B = sodium benzoate, C = sodium citrate

Then all possible combinations of 3 hydrotropic agents were used to determine the solubility so that total concentration was again 40 %, but individual concentration was 13.3 % w/v (Table 10).

Table 10: Equilibrium solubility of furosemide in different hydrotropic blends

S. No.	Combination	Total Conc. (%w/v)	Individual conc. (%w/v)	Solubility (%w/v)	Solubility enhancement ratio
1	U +A +B	40.00	13.33	1.918	239.756
2	U+A +C	40.00	13.33	0.243	30.375
3	A+B +C	40.00	13.33	0.926	115.754
4	U+B+C	40.00	13.33	3.958	494.752

Where, U= urea, A= sodium acetate, B = sodium benzoate, C = sodium citrate

The blend with maximum solubility enhancement (U+B+C) was further explored by changing the ratio so that maximum solubility can be obtained (Table 11).

Table 11: Equilibrium solubility of furosemide in different hydrotropic blends

S. No.	Combination	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1	U+B+C	40.00	10:20:10	4.782	597.751
2	U+B+C	40.00	10:10:20	1.934	241.759
3	U+B+C	40.00	15:20:5	5.285	660.625
4	U+B+C	40.00	5:20:15	3.405	425.625

Where, U= urea, A= sodium acetate, B = sodium benzoate, C = sodium citrate

Finally, combinations of four hydrotropic agents were used to determine the solubility so that total concentration was again 40 %, but ratio of individual agent was 10: 10: 10: 10. This blend was also further explored by changing the ratio so that blend with maximum solubility can be obtained Table 12.

Table 12: Equilibrium solubility of furosemide in different hydrotropic blends

S. No.	Combination	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1	U+A+B+C	40.00	10:10:10:10	1.183	147.875
2	U+A+B+C	40.00	5: 5: 10: 20	1.953	244.125
3	U+A+B+C	40.00	5: 20: 10: 5	1.132	141.575
4	U+A+B+C	40.00	20: 5: 10: 5	3.085	385.625
5	U+A+B+C	40.00	10: 5: 20: 5	4.524	565.529
6	U+A+B+C	40.00	15: 5: 15: 5	4.247	530.875

Formulation of Hydrotropic Solid Dispersions of Furosemide

As evaporation proceeded, speed of rice bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet).

Table 13: Composition of hydrotropic solid dispersion

S. No.	Drug: Hydrotrope blend	Quantity taken (gm)			
		Furosemide	Urea	Sodium Benzoate	Sodium Citrate
1	1:6	1.00	2.25	3.00	0.75
2	1:8	1.00	3.00	4.00	1.00
3	1:10	1.00	3.75	5.00	1.25
4	1:12	1.00	4.50	6.00	1.50

The wet solid dispersion thus obtained were spread on several watch glasses and the watch glasses were kept in hot air dry oven maintained at 50± 2ºC so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through sieve # 60 and were finally stored in an air tight glass bottle. Same procedure was utilized to prepare hydrotropic solid dispersion in the ratio of 1:8, 1:10, 1:12, using appropriate quantity of hydrotropic agents (Table 13).

Determination Of Drug Content In Solid Dispersion And In Physical Mixture

Table 14: Drug content of Furosemide in solid dispersions or physical mixture

S. No.	Drug: Hydrotrope blend	Drug content (mg)	
		Solid dispersion	Physical mixture
1	1:6	20.33	20.07
2	1:8	19.60	21.19
3	1:10	20.73	19.60
4	1:12	18.68	20.53

Further 1 ml of the above solution was diluted upto 10 ml with demineralized water and absorbance of this solution was measured at 333 nm against corresponding reagent blank. The analysis was carried out in triplicate and drug contents were determined. Results of the analysis are shown in the Table 14.

Dissolution Rate Studies

Calculations for the amount of drug were done using respective regression equations and the results of the dissolution studies are shown from Table 15-24.

Table 15: Dissolution rate studies of solid dispersion of 1: 6 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.336	22.192	19.972	99.864
2	5	0.334	22.059	19.853	99.268
3	10	0.329	21.728	19.555	97.778
4	20	0.330	21.794	19.615	98.076
5	30	0.329	21.728	19.555	97.778

Table 16: Dissolution rate studies of solid dispersion of 1: 8 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.329	21.7211	19.552	97.775
2	5	0.331	21.860	19.674	98.374
3	10	0.329	21.661	19.493	97.484
4	20	0.328	21.664	19.498	97.489
5	30	0.326	21.259	19.376	96.688

Table 17: Dissolution rate studies of solid dispersion of 1: 10 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.338	22.324	20.092	100.461
2	5	0.334	22.059	19.853	99.268
3	10	0.335	22.125	19.913	99.566
4	20	0.329	21.728	19.555	97.779
5	30	0.331	21.860	19.674	98.374

Table 18: Dissolution rate studies of solid dispersion of 1: 12 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.328	21.663	19.495	97.482
2	5	0.326	21.529	19.375	96.885
3	10	0.326	21.529	19.377	96.883
4	20	0.327	21.596	19.436	97.183
5	30	0.324	21.397	19.257	96.288

Table 19: Dissolution rate studies of physical mixture of 1: 6 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.121	7.953	7.158	35.793
2	5	0.165	10.867	9.780	48.905
3	10	0.198	13.052	11.747	58.738
4	20	0.232	15.301	13.774	68.870
5	30	0.243	16.033	14.429	72.141

Table 20: Dissolution rate studies of physical mixture of 1: 8 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.118	7.754	6.979	34.89
2	5	0.143	9.410	8.469	42.347
3	10	0.207	13.649	12.284	61.420
4	20	0.219	14.44	12.993	64.996
5	30	0.254	16.761	15.085	75.427

Table 21: Dissolution rate studies of physical mixture of 1: 10 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.184	12.125	10.913	54.666
2	5	0.197	12.986	11.688	58.440
3	10	0.234	15.437	13.893	69.466
4	20	0.268	17.688	15.919	79.599
5	30	0.295	19.476	17.529	87.645

Table 22: Dissolution rate studies of physical mixture of 1: 12 ratio

S. No.	Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug Dissolved
1	1	0.159	10.470	9.423	47.11
2	5	0.184	12.125	10.913	54.566
3	10	0.269	17.754	15.979	79.897
4	20	0.273	18.019	16.217	81.089
5	30	0.311	18.152	16.337	81.685

Table 23: Comparative account of different ratios of solid dispersions

S. No.	Time (min)	Cumulative percent Dissolved			
		1:6	1:8	1:10	1:12
1	1	97.48	97.77	100.46	97.48
2	5	96.88	98.37	99.268	96.88
3	10	96.88	97.48	99.566	96.88
4	20	97.18	97.48	97.77	97.18
5	30	96.34	96.688	98.374	96.288

Table 24: Comparative account of different ratios of physical mixture

S. No.	Time (min)	Cumulative percent Dissolved			
		1:6	1:8	1:10	1:12
1	1	35.79	34.89	54.666	47.11
2	5	48.90	42.347	58.440	54.566
3	10	58.738	61.420	69.466	79.897
4	20	68.870	64.996	79.599	81.089
5	30	72.14	75.427	87.645	81.685

From the above studies, it is evident that all the ratios of solid dispersions were dissolved completely within 1 minute, and when observed visually, they were found to be dissolved only within 10-20 seconds. While, on the other hand, none of the physical mixture dissolved completely even after 30 minutes. Since there was no significant difference in dissolution rate of different ratios of solid dispersions, therefore 1: 6 ratio was considered to be optimum ratio and was used for further studies.

Micromeritic Properties Of Solid Dispersions

I. Compressibility index (CI)

It was calculated using the following formula, and recorded in Table 27

$$C.I. = \{(V_o - V_f)/V_o\} \times 100$$

Where, V_o = Initial volume of untapped powder, V_f = Tapped volume

II. Hausner ratio

Tapped density and bulk density were measured and the Hausner ratio was calculated using the following formula, and recorded in Table 27.

$$\text{Hausner ratio} = D_f / D_o,$$

Where, D_o = Bulk density, D_f = Tapped density

Table 25: Relationship of compressibility index and Hausner ratio with powder flow

% compressibility	Hausner Ratio	Flowabilty
<10	1.00-1.11	Excellent
11-15	1.12-1.18	Good
16-20	1.19-1.25	Fair
21-25	1.26-1.34	Passable
26-31	1.35-1.45	Poor
32-37	1.46-1.59	Very poor
>38	1.60	Very, very poor

Angle of repose

Table 26: Relationship between angle of repose and powder flow

Angle of repose (degree)	Flowability
25- 30	Excellent
31 –35	Good
36 -40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very, very poor

Table 27: Results of micromeritic properties of solid dispersions

S. No.	Parameter	Result
1	Bulk Density (gm/cm^3)	0.704
2	Tapped Density (gm/cm^3)	0.847
3	Compressibility Index	16.901
4	Hausner Ratio	1.203
5	Angle of repose	32º

The closeness of values of bulk density and tapped density indicates the free flowing property of solid dispersions. The values of compressibility index, Hausner ratio and angle of repose indicate that the flow character of solid dispersion is fair and no aid is needed to increase the flow properties.

Powder X-Ray Diffraction Studies

The X.R.D. pattern of furosemide shows intense and sharp peaks that prove crystalline nature of furosemide. Also X.R.D. patterns of solid dispersion and physical mixture gave sharp and intense peaks and are thus easily comparable with that of furosemide. The diffraction pattern of solid dispersion and physical mixture showed some peaks at 2Ɵ of 18.0, 18.9, 27.7 and 28.6 which are characteristic of pure furosemide.

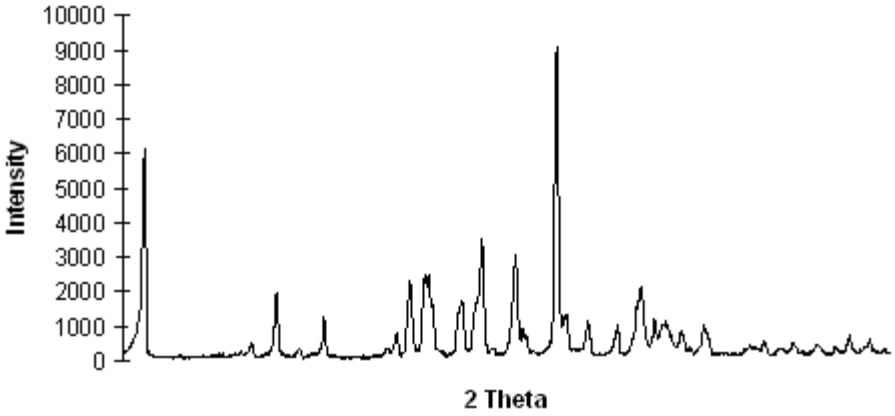

Fig. 3: X.R.D. spectra of pure furosemide

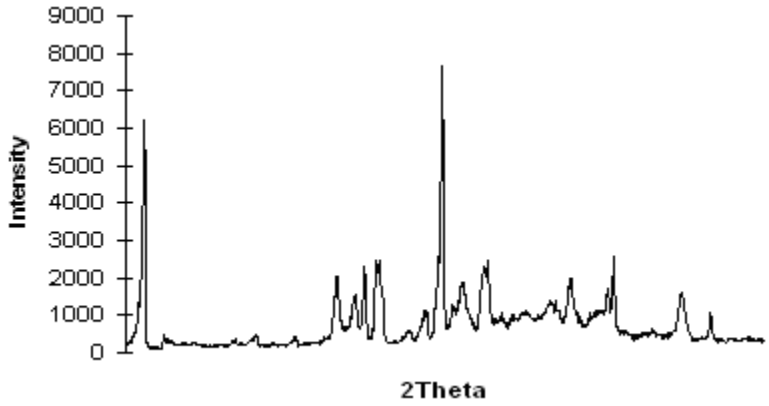

Fig. 4: X.R.D. spectra of 1:6 physical mixture

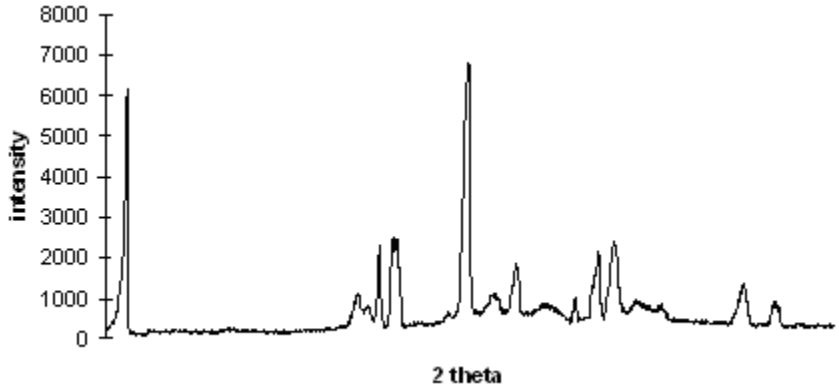

Fig. 5: X.R.D. spectra of 1:6 solid dispersions

Since the diffraction pattern of solid dispersion and physical mixture showed some peaks at 2Ɵ of 18.0, 18.9, 27.7 and 28.6 which are characteristic of pure furosemide,[46] therefore it can be presumed that formation of hydrotropic solid dispersion or physical mixture does not cause any physical and chemical interaction between furosemide and hydrotropes at molecular level.

Differential Scanning Calorimetric Studies

In order to obtain the DSC thermo grams of the drugs and their formulations (HSD and PM), a thermal analysis instrument, TA Instruments-2910 modulated DSC (USA) was employed. To carry out these studies, 4 mg of drug or formulation of drug was weighed accurately and placed in one of the matched aluminum pan. The sample pan and the reference pan both were sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10ºC/min with a continuous purge of nitrogen (45 CC/min) was done with recording of energy changes in the sample with respect to the reference in the temperature range of 80-200ºC. Various DSC thermo grams (melting isotherms) are shown in Fig. 6-9.

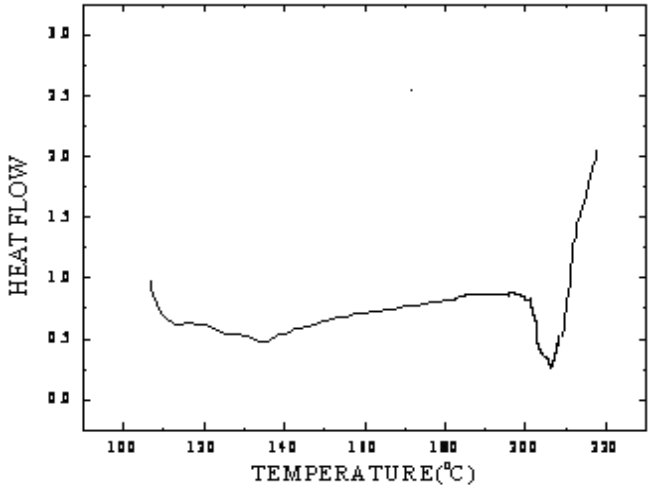

Fig. 6: D.S.C. curve of Furosemide

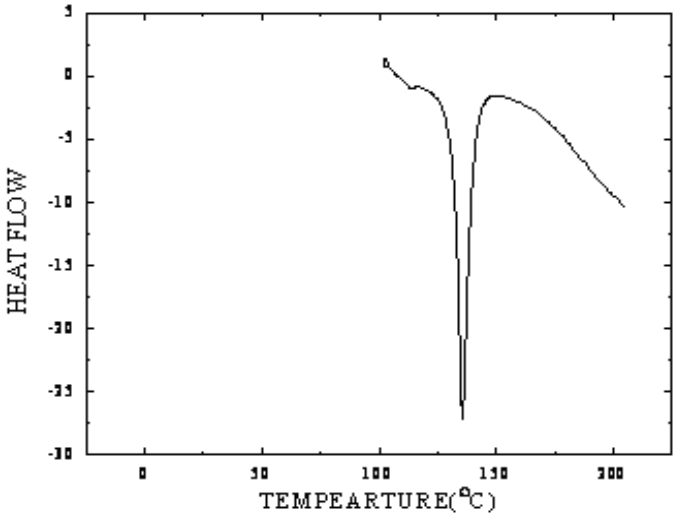

Fig. 7: D.S.C. curve of urea

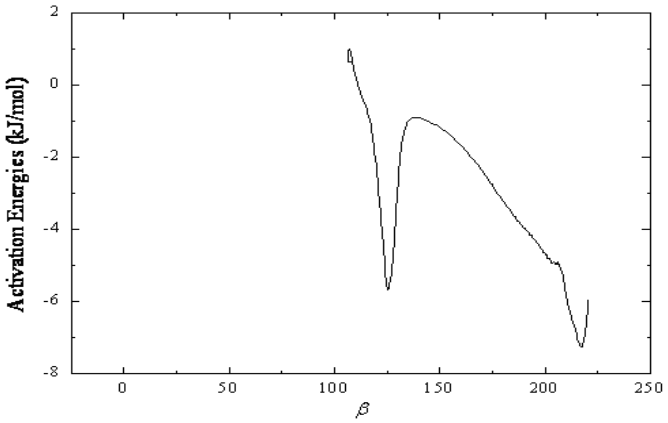

Fig. 8: D.S.C. curve of 1:6 physical mixture

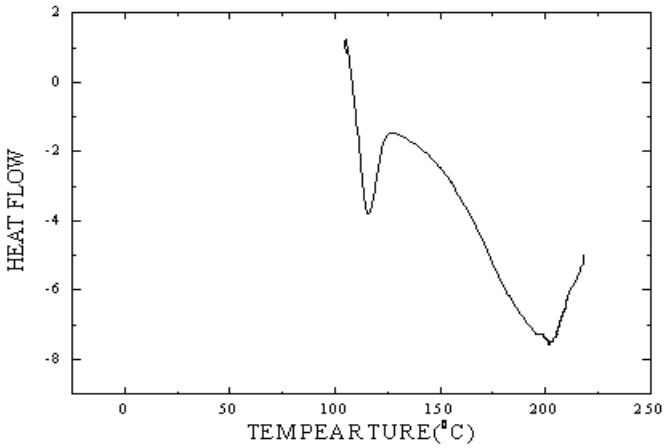

Fig. 9: D.S.C. curve of 1: 6 solid dispersion

D.S.C. curve of urea showed sharp endothermic peaks at 136º C and D.S.C. curve of Furosemide showed sharp endothermic peak at 207º C. While the D.S.C. curve of physical mixture and solid dispersion both showed endothermic peak near 137ºC and 207ºC which indicates the absence of any complex formation in case of solid dispersion or physical mixture. Only difference between D.S.C curve of hydrotropic solid dispersion and physical mixture was that endothermic peak in case of physical mixture was found to be relatively sharp and more intense as compared to that of solid dispersion.

Scanning Electron Microscopy

S.E.M. was used to investigate solid state physical structure of the prepared solid dispersions. S.E.M. photographs of Furosemide, its physical mixture with hydrotropic agents and its solid dispersions were obtained using a scanning electron microscope model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV. (Fig. 10-13)

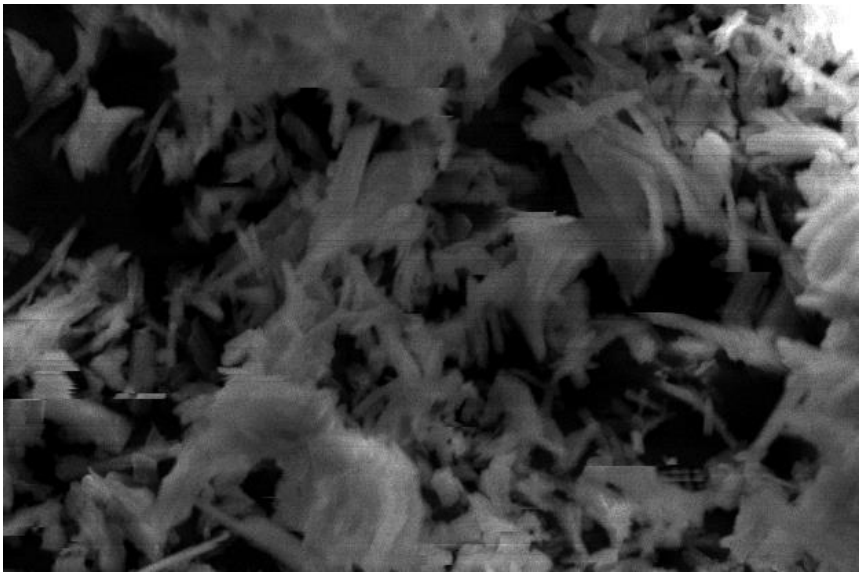

Fig. 10: S.E.M. photographs of pure Furosemide

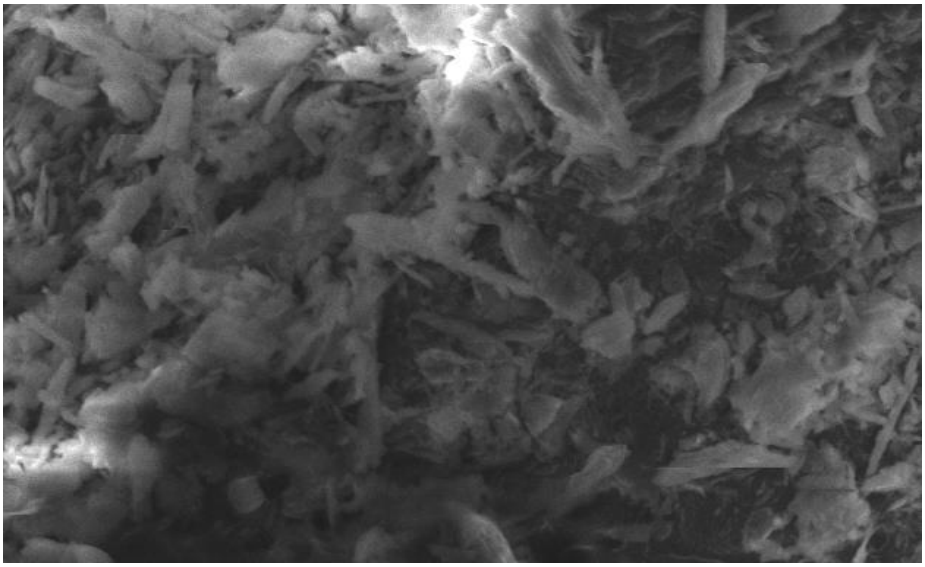

Fig. 11: S.E.M. photograph of physical mixture of Furosemide with Hydrotrope

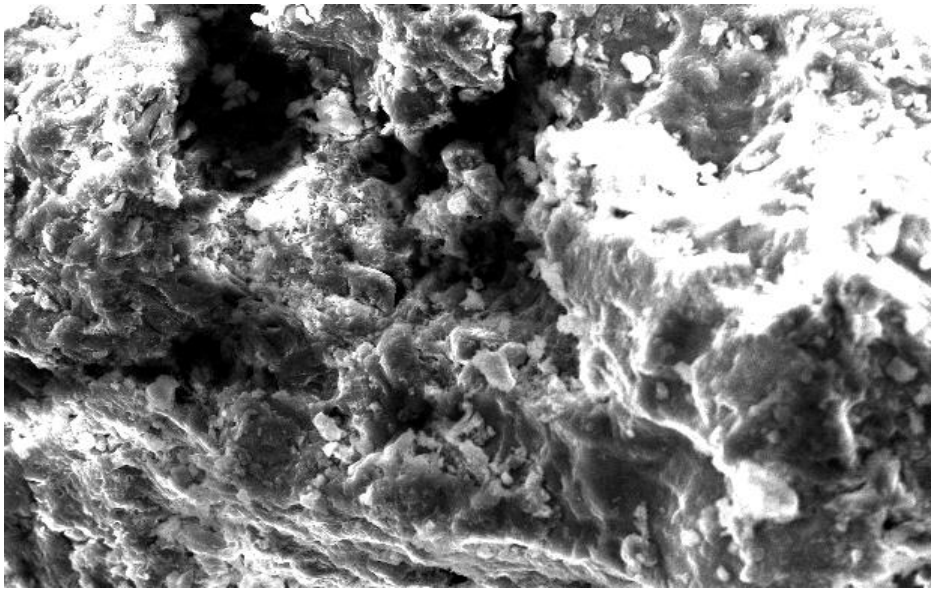

Fig. 12: S.E.M. photograph of hydrotropic solid dispersion of Furosemide

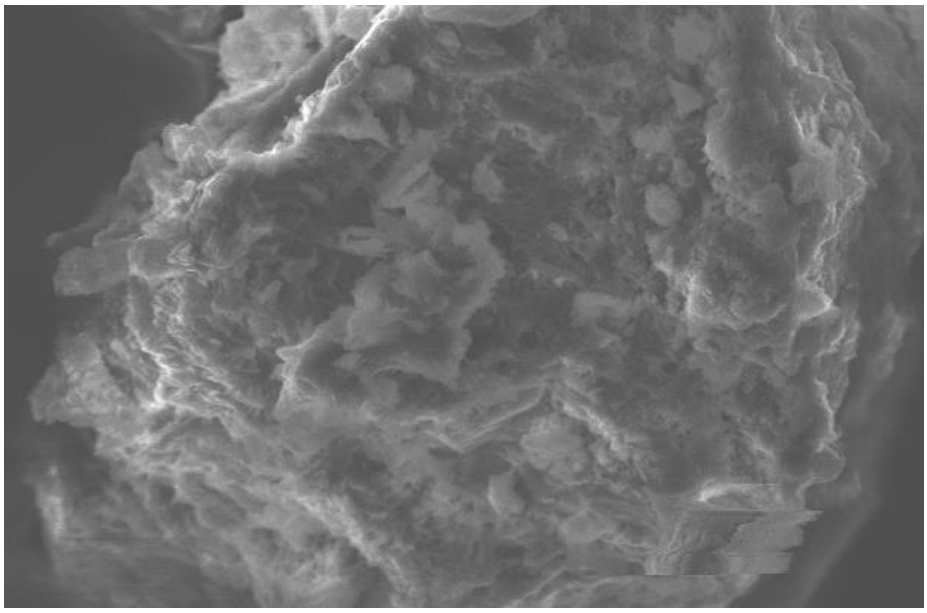

Fig. 13: S.E.M. photograph of hydrotropic solid dispersion of Furosemide

S.E.M. photographs of pure Furosemide (Fig. 10) show characteristic needle shaped structures, indicating the crystalline of Furosemide. These needle shaped structures can also be seen along with other structures of hydrotropic agents in photographs of physical mixture (Fig. 11). But in photographs of solid dispersions, there are no distinguishable needle shaped structures of Furosemide (Fig. 12 and 13), suggesting the total miscibility of Furosemide within the carrier.

Conclusion

Hydrotropy is a novel, safe and effective way to enhance solubility of poorly aqueous soluble drugs. Immediate dissolution of practically insoluble drug i.e. Furosemide in aqueous dissolution media indicates it's great potential to solubilized the drug in biological fluids and thus appreciable enhancement in bioavailability and onset of action can be expected. Thus the concept of mixed Hydrotropy is an emerging field which can serve as a milestone for

solubility enhancement and therefore deserves an urgent attention of scientific community to asses it's efficiency and applicability.

Floating dosage forms can significantly prolong the gastric residence time of drugs and thus can improve bioavailability, reduces drug waste with new therapeutic possibilities and substantial benefit to the patients. There are many advantages of using optimization techniques while developing a formulation because it gives the researcher the ability to study interactions between factors.

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