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Research Article

Development and Evaluation of Dry Adsorbed Emulsion for Extended Release of Niacinamide

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ABSTRACT

Dry Adsorbed Emulsion was defined as an organised dispersion of hydrophilic and hydrophobic particles. The structure of this system is described by the construction of water-in-oil(w/o) emulsion. Niacinamide was dissolved in aqueous phase of primary water-in-oil emulsion as an active drug. The aqueous phase of w/o emulsion was adsorbed by an hydrophilic silica and the oil phase was adsorbed by a hydrophobic silica, to obtain solid free flowing granular form of the system. The DAE granular system was evaluated for its flowability and the effect of particle size. The effect of silicone oil in DAE found to exhibit promising results on the extended release of niacinamide as studied at pH1.2 stimulate the gastric respectively.

Keywords: Dry Adsorbed Emulsion; Particle size; Granular form; Extended release.

INTRODUCTION

DAE is "Dry Adsorbed Emulsion" is an organised dispersion of hydrophilic and hydrophobic particles whose structure is initiated by the structure of water-in-oil emulsion which is changed into a free flowing granular system by using two adsorbents silicas with suitable polarities.¹.

The role of each silica is defined as follows: The aqueous phase of the water-in-oil liquid emulsion and the active drug were adsorbed by the hydrophilic silica that produced a creamy liquid.² The addition of the hydrophobic silica changed the creamy liquid into a fluid powder that is the "dry adsorbed emulsion"³.

The "Dry Adsorbed Emulsion" containing a highly water soluble drug (i.e. Niacinamide) developed and evaluate for powder rheology and drug release kinetics. In vitro dissolution testing was performed under experimental conditions (medium at pH1.2 with or without lubricant addition, different particle sizes, large or mixed particles. The relevance of dissolution data was improved by lubricant addition (5.0% Magnesium Sterate). After an initial release from superfacial layer of DAE of niacinamide, the dissolution followed the Zero order release, Higuchi release and Krosemeyer peppas model release. This suggested that DAE behaved as a matrix system, which prolonged drug release by

diffusion through the hydrophobic part of the DAE. Drug –Polymer interactions in the solid state were studied by Fourier Transform Infra red spectroscopy (FTIR), differential scanning calorimeter (DSC) and UV spectroscopy. The aim of the present work was to develop and evaluate "Dry Adsorbed Emulsion" for prolongation of Niacinamide release.

MATERIALS

Niacinamide was received as a gift sample from Vasu Enterprises Pvt. Ltd. Ludhiana, Punjab,India. Hydrophilic Silica (Colloidal silicone di oxide IP) (Aerosil 200®) and Hydrophobic Silica (Precipitated silica Treated) (Aerosil R972®) was also received as a gift sample from Madhu Silica Pvt.Ltd. Bhavnagar, India. Silicone oil was also used from Rankem Lab, Delhi, India. Hydrochloric acid, Potassium chloride, chemicals used as analytical grade obtained from Loba chemical (P) Ltd, Mumbai, India and Magnesium sterate from Merck, Analytical Reagent, Mumbai, India.

METHODS

Selection of Drug

In the present study Niacinamide a hyperlipidemic drug was selected as a model drug after an extensive literature search. This drug was selected on the basis of its pharmacokinetic and toxic manifestations. The importance of these two properties lies in determinig oral absorption.

- 1. Class 1 drug requires no major challenge for its conversion into immediate release dosage forms.
- 2. If controlled release dosage form is needed it requires to slow down the drug release from the dosage form and reduce the drug absorption rate.

Preparation of Dry Adsorbed Emulsion (DAE) Kneading Method

DAE was prepared by the method of following process (Chambin et al., 2000). Hydrophilic silica (Aerosil 200[®]) was first blended with each of the lipid phase i.e. silicone oil. It was followed by the addition of purified water under a high mechanically stirring rate, which produced a W/O creamv emulsion where the drug (niacinamide) was dispersed. Magnesium sterate was added as a lubricant. Finally hydrophobic silica (Aerosil R972®) was added slowly until the cream changed into a paste and then into a free-flowing powder with various diameter size of the particles. Large (362-725um): Mixed (115-725um) for the two different forms.



Table 1: Flow Chart Showing Methodof Dry Adsorbed Emulsion Preparation

In the DAE formulation the amount of hydrophobic silica which can adsorbed 5ml of oil is 2.54gm and the amount of hydrophilic silica which can adsorbed 5ml of water is 1.5gm. Four formulations were made using the same procedure with or without addition of lubricant are as follows:

- FS51pz: DAE with Silicone oil large particle size formulation without lubricant (362-725µm).
- FS5mpz: DAE with Silicone oil mixed particle size formulation without lubricant (115-725µm).
- FS6lpz: DAE with Silicone oil large particle size formulation with lubricant (362-725µm).

FS6mpz: DAE with Silicone oil mixed particle size formulation with lubricant (115-725µm).

Derived Properties of DAE System Powder Flow Analysis

Micro particle were characterized for their micromeritic properties such as particle size, bulk density, tapped density, Hausner's ratio, % Carr's index and angle of repose. The particle posses should an adequate level of flowability when blending with ingredients in formulation to ensure.

Bulk Density = $\frac{\text{Mass of the DAE powder}}{\text{Bulk volume}}$ $\text{Tapped Density} = \frac{\text{Mass of the DAE powder}}{\text{tapped density}}$

Angle of repose

The angle of contact measured to determine the wetting property of a micro particulate carrier. It determines the nature of DAE in terms of hydrophilicity and hydrophobocity.

Angle of repose, Hausner ratio, and Carr index (% compressibility index) were determined to predict flowability. A higher Hausner ratio indicates greater cohesion between particles, while a high % Carr index is indicative of the tendency to form bridges. Angle of repose of the DAE, is the maximum angle possible between the surface of the pile of granules and the horizontal plane, was obtained by fixed funnel method using the formula⁴

Angle of repose = Tan θ h/r θ = Tan inverse h/r

The values were compared from the reference values of the tables

Table 2: Reference table Angle of repose

Angle of repose θ degrees	Flow property
<25	Excellent
25 - 30	Good
30 - 40	Fair to passable
>40	Very Poor

Hausner ratio and Carr's index were calculated using the formulae: and the values were compared from the reference values of the table.

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Hausner Ratio = \frac{Tapped density}{Bulk density}
Carr's index = \frac{True density-Bulk density}{True density}
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Table 3: Reference table Hausner's ratio

Hausner index values	Flow property
<1.25	Good
>1.25	Poor flow
1.25-1.5	Added glidant normally improves flow

Table 4: Reference table Carr's index

Carr's %	Flow property
5 – 15	Excellent
12 -16	Good
16-18	Fair to passable
23-35	Poor
33-38	Very Poor
>40	Very – very poor

Dissolution Method

In vitro dissolution studies of DAE were performed (in triplicate). The formulations were evaluated for their release profile using USP type II apparatus (paddle method) at 50rpm. The media used was 900ml pH1.2 buffer with slight amount of SLS (0.1%) maintained at 37±0.5°C. An accurately weighed amount of the prepared systems equivalent to 50mg of the drug (which is usual therapeutic dose) was added to each jar. The samples were drawn every 5 min during the first 30min then after every 15min for one hour (1h) and then 30min for one and half an hour(11/2hr) and then every hour up to six hour (6h). and filtered. The initial volume was maintained by adding 5ml of fresh dissolution medium. The samples were filtered through whatman filter paper no.41 and assayed spectrophotometrically 262nm using a double beam spectrophotometer (Hitachi, model AU 2701 spectrophotometer (Japan)).

Release kinetics

In order to understand the release mechanism of the Niacinamide from the prepared DAE systems. The release data were subjected to Zero order (Eq 1),

Higuchi model (Eq 2), and Krosmeyer peppas model (Eq 3). $Q_t - k_0 t$ (1), $Q_t = kt^{\frac{1}{2}}(2)$ and $M^t/M^{\alpha} = kt^n(3)$. Where Q_t is the percent of drug released at time t, Q_0 is the intial amount of drug present in the DAE, M^t/M^{α} is the fraction of drug release, n is the release exponent and k is the constant of equations. Dissimilarity and similarity factors were calculated for comparison of prolonged release formulations and tab. Nialip.⁵.

RESULTS

Physicochemical properties of pure drug Niacinamide

Appearance

Niacinamide were found to be white crystalline powder.

Melting point

The observed melting point of pure drug Niacinamide was134.17°C determined by digital melting point apparatus (Lab India-MR-VIS, Mumbai) by capillary method

Solubility

Solubility of Niacinamide was found to be freely soluble in water. An excess amount of niacinamide (5gm) was added to 5ml distilled water. Filtered and the Filtrate was appropriately diluted for recording absorbance. The solubility was found to be pure drug is 600mg/ml.

UV Scan of pure drug Niacinamide in 0.1N HCl pH 1.2 buffer

The absorption maxima (λ_{max}) of Niacinamide in pH1.2 buffer were observed to be at 262 nm (reported $\lambda_{max} = 262$ nm, IP-1996).

Preparation of Standard curves In pH 1.2 Buffer or 0.1N HCl

Standard curve of Niacinamide in 0.1N HCl was prepared .This shows linear relation between concentration and absorbance (follows Beer Lambert Law) so these equations can be used to calculate unknown concentration of Niacinamide in solution when absorbance is known at respective wavelength.



Fig. 1: Shows Standard Curve of Niacinamide drug in 0.1N HCl (pH 1.2)

Derived properties of DAE formulationHausnerSieve analysis of DAE FormulationsdensityThe flow properties of granules were characterizedHausner

in terms of angle of repose, Carr's index and

Hausner's ratio. The bulk density and tapped density were determined and from this data Hausner's ratio and Carr,s index were calculated.

Table 5: Powder characterisation and reconstitution properties of Silicone oil DAE with mixed particle size formulation (FSmpz) with or without lubricant

S. no	DAE Formulation code	Weight of the DAE Formulation (gms)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Hausner's Ratio(%)	Carr's Index (%)	Angle of repose(°)
1	FS5mpz	10.00	0.434	0.37	1.16	14.6	28.17
2	FS6mpz	10.00	0.478	0.470	1.19	16.61	29.75

Formulation code

(i) FS5 (Silicone oil + drug) (ii) FS6 (Silicone oil + drug + lubricant).

Lubricant – Magnesium sterate, FS (Silicone oil formulation)

Table 6-7 shows the sieving results obtained from a powdered sample exhibiting a percentage

cumulative weight retained. The data are typically presented by listening them as a function of both the sieve mesh number are associated sieve size opening (in mm). For each sieve in the nested series, the mass of sample retained on each sieve, the percentage of sample retained on each sieve were calculated.

Table 6: Sieving results of DAE with Silicone oil mixed particle size formulation (FS5mpz) without lubricant

S.no	Seive no.	Arithmetic mean size of opening (mm)	Wt.retained on a sieve (g)	% Wt. retained	Cumulative % wt. retained	Avg.particle size(% wt. retained x Avg. size opening)x100 (mm)
1	14/16	1.29	0.598	6.573	6.573	8.479
2	16/20	1.015	1.415	15.554	22.217	15.787
3	20/30	0.725	1.42	15.609	37.736	10.925
4	30/40	0.512	2.067	22.721	60.457	11.633
5	40/50	0.362	1.498	16.466	77.023	5.96
6	50/70	0.256	0.838	9.211	86.234	2.358
7	70/80	0.196	0.42	4.616	90.85	0.904
8	80/100	0.165	0.33	3.627	94.477	0.598
9	100/120	0.137	0.311	3.418	97.895	0.468
10	120/150	0.115	0.182	2	99.895	0.23
	Total		9.097			Total = 57.342
						Avg. Diameter(mm)=0.57342

S.no	Seive no.	Arithmetic mean (mm)	Wt.retained on a sieve(g)	% Wt. retained	Cumulative % wt. retained	Avg.particle size(% wt. retained x Avg. size opening)x100 (mm)
1	14/16	1.29	1.647	13.025	13.025	16.802
2	16/20	1.015	2.169	17.154	30.179	17.411
3	20/30	0.725	2.611	20.65	50.829	14.971
4	30/40	0.512	2.69	21.274	72.103	10.89
5	40/50	0.362	1.179	9.324	81.337	3.375
6	50/70	0.256	0.93	7.355	88.692	1.882
7	70/80	0.196	0.526	4.16	92.852	0.815
8	80/100	0.165	0.375	2.823	95.675	0.465
9	100/120	0.137	0.265	2.095	97.77	0.287
10	120/150	0.115	0.25	1.977	99.747	1.01
	Total		12.644			Total = 67.908
						Avg. diameter (mm) = 0.679



Fig. 2: Graphical presentation data shows the percentage weight retained of DAE with Silicone oil mixed particle size formulation without lubricant (FS5mpz)



Fig. 3: Graphical presentation data shows the percentage weight retained of DAE with Silicone oil mixed particle size formulation with lubricant (FS6mpz)



Fig. 4: Graphical presentation shows the percentage cumulative weight retained of DAE Silicone oil mixed particle size formulation without Lubricant (FS5mpz)





	able 8: Average Particle size diameter of Silice	one oil mixed
particle size DAE formulation with or without lubricant		

DAE Formulation codes	Average particle size diameter r(mm)
FS5 mpz	0.57342
FS6 mpz	0.67908





In- vitro drug release results Figure 7 Shows DAE with Silicone oil large particle size (362-725 µm) formulation (FS6lpz) with lubricant at pH1.2



Fig. 7(a): Zero order release at pH 1.2



Fig. 7(b): Higuchi model release at pH 1.2



Fig. 7(c): Korsemeyer Peppas model release at pH 1.2





Fig. 8 (a): Zero order release at pH 1.2



Fig. 8(b): Higuchi model at pH 1.2



Fig. 8(c): Korsemeyer Peppas model release at pH 1.2





Fig. 9(a): Zero order release at pH 1.2



Fig. 9(b): Higuchi model release at pH 1.2



Fig. 9(c): Korsemeyer Peppas model release at pH 1.2





Fig. 10(a): Zero order release at pH 1.2



Fig. 10(b): Higuchi model release at pH 1.2



Fig. 10(c): Korsemeyer Peppas model release at pH 1.2





Fig. 11(a): Zero order release at pH 1.2



Fig. 11(b): Higuchi model release at pH 1.2



Fig. 11(c): Korsemeyer Peppas model release at pH 1.2

DISCUSSION

Niacinamide was got dissolved in a few minutes only in experimental conditions (3000mg of drug in 5ml of distilled water). When included in DAE, the Niacinamide dissolution was drastically much slower in formulations:

- DAE with Silicone oil large particle size formulation FS6lpz with lubricant Fig 7 (a) (b) (c).
- DAE with Silicone oil mixed particle size formulation FS6mpz with lubricant Fig 8 (a) (b) (c).

It is suggested that Niacinamide was presented, in the DAE particle, as dispersion surrounded by hydrophobic silica and magnesium sterate (as a lubricant). Such drug dispersion is expected to give Higuchian dissolution profile as shown in Fig 7 (b) & 8 (b).

An extended release was also obtained from formulations:

- DAE with Silicone oil large particle size formulation FS5lpz without lubricant Fig 9 (a) (b) (c).
- DAE with Silicone oil mixed particle size formulation FS5mpz without lubricant Fig 10 (a) (b) (c).

Thus, the DAE could be considered as an extended release pharmaceutical form particularly with the 362-725µm (large particle size), 115–725µm (mixed particle size), since, the niacinamide release lasted for several hours (Fig 7). This include that the DAE structure is described as a hydrophilic nucleus with the drug coated by a lipidic phase. Niacinamide a highly water soluble drug, an extended release was observed which is explained by the joint use of a hydrophilic silica and a hydrophobic silica. The latter modified the physico-chemical properties of particles which did not wet easily in dissolution medium and reduced the drug release rate by the combined effect of

hydrophobic silica and magnesium sterate . Each part included liquid phases (aqueous and oily) trapped in the silica of the same polarity by weak bonds (hydrogen or hydrophobic bonds). The drug was dispersed in each of them. Dissolution results strengthened this model structure: a part of niacinamide was immediately released from superficial layer, and the remaining drug was slowly delivered from hydrophobic parts.

On the contrary, the niacinamide release depended on the particle size: The theory of solid drug dissolution and Noyes Whitney equation (<u>Buckton and Beezer, 1992</u>) explains this fact: a reduction of particle size increases the surface area which results in a more rapid dissolution process by enhancing the solid–liquid interface (<u>Hintz and</u> Johnson, 1989).

Furthermore, the Higuchi and Korsmeyer peppas model fitted well to Niacinamide release data with linearity close to 0.9, in the case of

- FS6lpz: DAE with Silicone oil large particle size formulation with lubricant (362-725µm).
- FS6mpz: DAE with Silicone oil mixed particle size formulation with lubricant (115-725µm).
- FS5lpz: DAE with Silicone oil large particle size formulation without lubricant (362-725µm).

This confirming that the DAE could be classified as a matrix with a delivery mechanism controlled by Drug Diffusion.

Thus dry emulsions can be presented as a potential oral drug delivery system. Considering the physical and microbiological instability of usual emulsions, a dry emulsion (used as a powder) appears to be of interest of the formulator. DAE particle formulations had a good flowability in:

➢ Hausner's Index:

1.16 in FS5 mixed particle size DAE with Silicone oil without lubricant.1.19 in FS6 mixed particle size DAE with Silicone oil with lubricant.

> Carr's Index:

14.6 in FS5 mixed particle size DAE withSilicone oil without lubricant.16.6 in FS6 mixed particle size DAE withSilicone oil with lubricant.

> Angle of repose:

28.17 in FS5 mixed particle size DAE with Silicone oil without lubricant.

29.75 in FS6 mixed particle size DAE with Silicone oil with lubricant.

The study of FTIR spectra of drug loaded DAE demonstrated the characteristic absorption peaks for N-H stretch, sharp, amides at 3366 cm⁻¹, 3161 cm⁻¹, carbonyl group at 1680 cm⁻¹ C=O stretch of carboxyl amide at1698 cm⁻¹, C=O stretching, strong in amides at 1028 cm⁻¹, N-H bending in amide, C=N conjugated cyclic stretching 1592 cm⁻¹.

The DSC curve of the pure drug and the drug loaded DAE were shown in figure It is evident from the DSC profile that the pure Niacinamide exhibited a sharp peak at 134.175 °C which correspond to the melting point of the pure drug. The DSC profile of the drug loaded DAE showed a sharp peak at temperature corresponding close to the pure drug. It may be due to slight reduction in the crystalinity.

Three equations were used to release kinetics from the dry adsorbed emulsion and market formulation tablet Nialip CR 500mg results are reported in the above Figures (6 to 11). The data obtained from the release were fitted to various kinetic equations to determine the mechanism of drug release and

release rate. As indicated in DAE with Silicone oil large particle size formulation with lubricant (362-725µm) (FS6lpz) or DAE with Silicone oil mixed formulation with lubricant particle size (FS6mpz)(115-725µm) or market formulation tablet Nialip CR by higher correlation coefficient linearity close to 0.9. To confirm the release mechanism, the data were applied to Korsmeyer-Peppas equation to find out the release exponent *n*, which indicates the mechanism of drug diffusion. The data were well fitted with equation as indicated by high correlation ($R^2 = 0.9$) coefficient and the mechanism of Niacinamide release from formulation silicone oil DAE mixed particle size and large particle size formulation with lubricant was found to be non-Fickian diffusion (anolamous 0.5<n<.1).

DRUG AND EXCIPIENT INTERACTION

In Preformulation studies drug and excipient interaction were studied. The Dry Adsorbed Emulsion formulations of Silicone oil with or without lubricant were analysed for chemical and physical interaction using FTIR and DSC.

Fourier Transfer Infra Red (FTIR) Analysis

The FTIR analysis of Silicone oil used in DAE formulation with drug and with or without lubricant scanned in the range of 500-4000cm⁻¹ gave characteristic absorption peaks of 3370, 1699, 1681, 1620 and 1593 as compared to absorption peaks of 3366, 1698, 1680, 1618, and 1592 for pure drug niacinamide indicates that there is no chemical interaction between Silicone oil DAE formulation with or without lubricant has been shown in table 6.18. In other FTIR spectrum studies there is no significant peak shift was observed in DAE formulations and pure drug which confirmed absence of chemical interaction Niacinamide and Silicone oil DAE formulation.

 Table 9: Comparative Absorption Peaks of Pure drug Niacinamide and
 Silicone oil DAE formulation with or without lubricant

	Wave number (cm ⁻¹)		number (cm ⁻¹)		
S. No.	DAE Formulations	Pure Drug	Absorbance Assignment		
	FS5 & FS6	0			
1	3370	3366	N-H stretch, sharp, amides due to symmetric		
2	1699	1698	C=O strech of carboxyl amide		
3	1681	1680	C=O stretch of carbonyl group (symmetric)		
4	1620	1618	N-H bending in amide		
5	1593	1592	C=N conjugated cyclic stretching		

Table 10: FTIR Absorption peaks of Silicone oil DAE formulation with or without lubricant (FS5 & FS6)

S.no.	Wave number (cm ⁻¹)	Wave number (cm ⁻¹)	Absorbance Assignment (cm ⁻¹)
1	3500-3100	3370	N-H stretch, sharp, amides due to symmetric
2	2950-2550	2963	C-H stretch, sharp alliphatic
3	1800-1600	1698	C=O stretch of carboxyl amide
4	1760-1630	1681	C=O stretch of carbonyl group
5	1650-1580	1620	N-H bending in amide
6	1400-1000	1262	C-N stretching in primary aromatic amines



Fig. 12: FTIR Scan DAE of silicone oil large particle size formulation without lubricant (FS5)



Fig. 13: FTIR Scan of DAE silicone oil mixed particle size formulation with lubricant (FS6)

Differential Scanning Colorimetry (DSC) Analysis

DSC analysis of niacinamide and silicone oil DAE formulatioms were performed to confirm the absence of drug and silicone oil DAE mixed particle size formulation interaction. The DSC thermograms of the niacinamide(pure drug), formulation FS5 and formulation FS6 are shown in table 6.19. Crystalline nature of niacinamide was visible in the thermogram. However, no significant shift in endothermic peak was found in formulations of drug as compared with those of silicone oil DAE formulation mixed particle size.

 Table 11: Comparative endothermic peak of niacinamide drug with

 DAE Silicone oil mixed particle size formulations with or without lubricant

S.no.	Formulation Codes of DAE	Melting point(°C) of DAE formulations
1	PD (Niacinamide)	134.175
2	FS5 DAE	129.95
3	FS6 DAE	131.26

FormulationCodes

PD(Pure Drug),DAE(Dry Adsorbed Emulsion), F(Formulation),S5 (Silicone oil), S6 (Silicone oil + Lubricant),Lubricant (Magnesium sterate). The above data shows the pure drug (niacinamide) have melting point 134.175°C and the Silicone oil DAE formulation mixed particle size with lubricant having melting point near about the pure drug. This formulation gave promising results.



Fig. 14: DSC Scan of pure drug niacinamide



Fig. 15: DSC Scan of DAE silicone oil mixed particle size formulation without lubricant (FS5)



formulation with lubricant (FS6)

CONCLUSION

The result allow that DAE could be useful to produce a potential drug delivery system to improve the bioavailability in adjusting the drug dissolution rate at a biopharmaceutical level.DAE could be converted into capsule and tablet to achieve the required goal.

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