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SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT OF NATEGLINIDE BY SOLID DISPERSION TECHNIQUES

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ABSTRACT

In the present investigation, an attempt were made to improve the solubility and dissolution rate of a poorly soluble drug, Nateglinide by solid dispersion method using Urea, Dextrose and Mannito as Hydrophilic Inert carriers. Solid dispersion of Nateglinide was prepared by Kneading Method (KM), Solvent Evaporation Method (SEM), and Co-grinding Method (CM). In vitro release profiles of all Solid dispersions were comparatively evaluated and also studied against pure Nateglinide. Faster dissolution was exhibited by NDK_3, Solid dispersion containing 1:3 ratio of drug: Dextrose by Kneading Method. The prepared Solid dispersions were subjected for Drug Content, Infrared (I.R.) Spectroscopic Studies and Differential Scanning Calorimetry (DSC). FT-IR spectra revealed no chemical incompatibility between drug and Carrier. Drug - polymer interaction were investigated using differential scanning calorimetry (DSC). In addition to dissolution studies, XRD results revealed that Nateglinide was converted to its amorphous state. The dissolution rate of the prepared solid dispersion systems were determined in 0.1N Hydrochloric Acid Buffer pH 1.2 All the formulation showed marked improvement in the solubility and dissolution rate of drug which may be due to hydrophilic polymers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. The dissolution rate was enhanced in the following order KM > SEM > CM. The enhancement of dissolution rate may be due to increase in wettability, dispersibility as well as particle size reduction of the drug.

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INTRODUCTION:

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration[1-5]. Poorly water-soluble drugs present many difficulties in the development of pharmaceutical dosage forms due to their limited water solubility, slow dissolution rate and low bioavailability. The enhancement of oral bioavailability of poor

water soluble drugs remains one of the most challenging aspects of drug development[6]. Together with the permeability, the solubility behaviour and the dissolution rate of a drug is a key determinant of its oral bioavailability and is one of the most important concerning aspects of the pharmaceutical industries[6-8].

Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SDs) is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs[8]. Solid dispersions have been widely reported as an effective method for enhancing the dissolution rate and bioavailability of poorly water soluble drugs[9]. The dissolution rate is directly proportional to solubility of drug[10]. The term 'solid dispersion' refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the fusion, solvent evaporation and melt solvent methods[3]. The release mechanism of drug from a variety of solid dispersions depends on the physical properties of carriers as well as drug substances and preparation methods[9]. Solid dispersions have been used for a long time to solve many problems related to poor water solubility, low bioavailability and stability of many drugs[10-11]. Many procedures can be used to prepare solid dispersions such as fusion, solvent evaporations and solvent-fusion methods[12]. Other relevant methods can be used to prepare solid dispersions such as spray drying[13], freeze-drying[14] and microwaves[15]. Despite the great potential of solid dispersions for enhancing drug dissolution, the methods traditionally used have some problems such as physical instabilities of some drugs and difficulty in completely removing liquid solvent[16-17]. For drug delivery purposes, hydrophobic drugs may be solubilized within the core of the micelle or conjugated to the micelle- forming polymer. These amphiphilic copolymers are available in different grades as poloxamer 188 and poloxamer 407[18-20]. Poloxamer 407 was used to enhance the dissolution rate of several drugs such as atenolol[21], piroxicam[22] and ibuprofen[23-24].

The aim of the present investigation was to enhance the solubility, dissolution rate of Nateglinide with solid dispersion technique using Urea, Dextrose and Mannitol as a hydrophilic Inert carrier. Solid dispersion systems of the drug with Urea, Dextrose and Mannitol were prepared in different ratios by Kneading Method (KM) Solvent Evaporation Techniques (SEM) and Co-grinding Method (CM). The physicochemical properties of the prepared solid dispersion were evaluated using different methods.

Materials and Methods:

Nateglinide was supplied by Cadilla Health Care Pvt., Ltd, Ahmedabad. All other reagents were of analytical grade.

Preparation of Nateglinide Solid Dispersions (SDs) using different techniques:

Different drug: polymer ratios were used for preparing Nateglinide solid dispersions in Urea, Dextrose and Mannitol, *via* Solvent Evaporation Method (SEM), Co-grinding method (CM), and Kneading Method (KM).

Kneading Method (KM):

In this method, Nateglinide, Urea, Dextrose and Mannitol were weighed according to the drug and carrier ratios (1:1, 1:2 and 1:3) and were triturated using a small volume of Ethanol: Water (80:20) to give a thick paste, which was kneaded for 30 minutes and then dried at 40° C in an oven. NUK1 to NUK3 corresponds to preparations containing Urea, NDK1 to NDK3 Corresponds to preparations containing Dextrose and NMK1 to NMK3 Corresponds to preparations containgin Mannitol. The dried mass was then pulverized, passed through mesh no. 30, stored in a vacuum desiccator (48 hrs) and passed through sieve no. 60 before packaging in an airtight container.

Solvent Evaporation Method (SEM):

In this method, Nateglinide, Urea, Dextrose and Mannitol were weighed according to the drug and carrier ratios (1:1, 1:2 and 1:3) and dissolved in a common solvent, after complete dissolution of drug and carrier in Ethanol: Water (80:20), the solvent is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. NUS_1 to NUS_3 corresponds to preparations containing Urea, NDS_1 to NDS_3 Corresponds to preparations containing Dextrose and NMS_1 to NMS_3 Corresponds to preparations containgin Mannitol. The dried mass was then pulverized, passed through mesh no. 30, stored in a vacuum desiccator (48 hrs) and passed through sieve no. 60 before packaging in an airtight container.

Co-Grinding Method (CM):

In this method, Nateglinide, Urea, Dextrose and Mannitol were weighed according to the drug and carrier ratios (1:1, 1:2 and 1:3) and they were co-grinded with inert carrier for about 30hr in a glass mortar. The dried mass was then pulverized, passed through mesh no. 30, stored in a vacuum desiccator (48 hrs) and passed through sieve no. 60 to make various formulations before packaging in an airtight container. NUC_1 to NUC_3 corresponds to preparations containing Urea. NDC_1 to NDC_3 Corresponds to preparations containing Dextrose and NMC_1 to NMC_3 Corresponds to preparations containing Mannitol.

Characterization of Nateglinide - Carrier Mixture:

Solubility Study:

For determination of solubility of Nateglinide, excess amounts of drug were added to 10.0 mL Distilled Water, 2% w/v SLS, 0.1N HCL (pH 1.2), Phosphate Buffer (pH 7.4) sonicated for 1 h (J. P. Selectasa., Spain) and shaken in a shaker water bath with the temperature maintained at 37 °C for 48 h (SBS Instrument, Germany). The suspension was filtered (0.45 µm micro-filter), suitably diluted and analyzed spectrophotometrically at 210 nm for Nateglinide content.

Differential Scanning Calorimetry (DSC)

Calorimetric studies of the drug and the prepared solid dispersion systems were performed using a DSC-60 (Shimadzu, Kyoto, Japan). The 4– 5 mg samples were placed in hermetically sealed aluminum pans. A 10°C/ min scanning rate was used over the 25–200°C temperature range. Indium was used as the temperature and enthalpy standard.

Powder X-ray diffractometry (PXD)

Powder X-ray diffraction patterns of the drug-Carriers solid dispersions were compared to the individual components that were generated using a wide-angle Rigaku Ultima IV X-ray diffractmeter (Rigaku Corporation, Tokyo, Japan). The instrument was operated on the 2θ scale. The angular range was 10° to 50° (2θ) and counts were accumulated for 1 sec at each step.

***In-vitro* Dissolution Study:** The dissolution of Nateglinide from different samples was carried out in 900 mL Hydrochloric Acid buffer pH 1.2 maintained at 37±0.5°C under 50 rpm stirring rate (Electro Lab TDT – 08L). 100 milligrams of the drug or its equivalent in SD was dispersed on the surface of the dissolution medium. Five mL were withdrawn at appropriate time intervals, and filtered. The % cumulative amount of drug released with time was determined spectrophotometrically at 210 nm. Triplicate runs were carried out and the amount of drug dissolved was calculated.

Statistical Analysis:

All data were expressed as mean standard deviations (± SD). Statistical analysis was performed using student t-test at 0.01 level of significance.

RESULTS AND DISCUSSION

To investigate the potentiality and performance of Urea, Dextrose and Mannitol based systems for enhancement of drug solubility and dissolution, the solid dispersion of Nateglinide-Urea, Nateglinide-Dextrose and Nateglinide-Mannitol binary systems were prepared by different methods. These techniques include, Kneading Method and Solvent Evaporation Method, Co-grinding Method.

Characterization of prepared Solid Dispersion:

Solubility Analysis:

The solubility profile of Nateglinide in various solvents are shown in table -1. The solubility of Nateglinide in water was found to be approximately 30µg/ml. Significantly, an increase in solubility of Nateglinide with 0.1N HCL (pH 1.2) and Phosphare Buffer (pH 7.4). Table -1. Maximum solubility was observed in Hydrochloric Acid pH 1.2. So 0.1N HCL (pH 1.2) was selected for estimation of drug content and also performed in-vitro dissolution in the same media.

FTIR:

The figure – 1, shows the FTIR spectra of Nateglinide, Urea, Dextrose, Mannitol, and solid dispersion systems. The infrared spectrum of pure Nateglinide exhibited the characteristic bands corresponding to the functional groups of the drug at 3,433 cm^{-1} (due to the mutual overlapping of NH and OH stretching), 1,651 cm^{-1} (corresponds to the C = O stretch), 1,620 cm^{-1} (corresponds to NH bending), and 1,354 cm^{-1} (corresponds to CN stretching). Solid dispersions showed the characteristics peaks of Nateglinide with decreased intensity and little

shifting of peaks. The IR spectrum of dispersion shows shifting of the characteristic peak of N-H from 3429 to 3419 due to hydrogen bonding. However the IR spectrum does not showed any additional peak indicating the absence of any chemical interaction between Nateglinide and hydrophilic inert carriers. From the above data it was assumed that physical interaction of drug with polymer is responsible in dissolution enhancement. Figure - 1 indicates that drug and excipient (polymer) interaction was not seen in the formulation.

DSC:

Differential scanning calorimetry (DSC) is frequently used in the pharmaceutical field as a thermal analysis technique, to provide detailed information about both the physical and energetic properties of substances. The thermal behaviour of Nateglinide, Nateglinide-Urea, Nateglinide-Dextrose, Nateglinide-Mannitol solid dispersion systems prepared by different methods and carriers are shown in Figure - 2. Nateglinide displayed an endothermic peak at 140 °C corresponding to its melting point. Urea, Dextrose and Mannitol showed endothermic peak at 160^0C, 100^0C and 120°C due to its melting point. Thermal traces for Solid dispersion at 1:3 ratio showed very weak peak shifted to lower melting point. The peak appeared at 140°C with heat of fusion -76.3 mJ and -68.5 mJ respectively for the ratio 1:3 with lower intensity of peak appearance in case of Kneading Method. The decrease of the intensity of the peak may be due to the dilution effect by the carrier used. Other SD systems prepared using different drug: polymer ratios showed the disappearance of the characteristic peak of the drug. This may be due to decreased crystallinity of the drug. These results were in agreement with that found by Shin and Cho. It is worthy to note that the heat of fusion for all solid dispersions systems decreased which might indicate that Nateglinide has been transformed to an amorphous or less crystalline form in its-polymer Solid Dispersion systems.

XRD:

Figure – 3, show XRD Photographs of pure drug and formulations. XRD study reveals the physical interaction between the drug and polymers. Nateglinide is a highly crystalline powder with several characteristic diffraction peaks that appeared at diffraction angle 2θ (6.0, 13.0, 14.2, 19.1, 22.1 and 26.2). All prepared dispersions showed changes in the number of peaks or few diffuse peaks were observed in all dispersions as compared to XRD spectra of raw Nateglinide drug, which indicate decrease in crystallinity in dispersed Nateglinide. The intensities of the major drug peaks of Nateglinide were slightly decreased in Solid Dispersions of Kneading Method ratio 1:3. But the most of drug peaks were disappeared in all different solid dispersion systems. This means that in Solid Dispersion, the drug was still in a crystalline state but the intensity was decreased due to the dilution effect of the carrier, but in all Solid Dispersion systems the disappearance of the characteristic peaks of drug may be due to change into amorphous one, as observed in the DSC studies. The decreased drug crystallite size can explain the faster dissolution and increased solubility, which indicates that there is physical interaction between drug and polymers.

Drug Content Analysis:

The drug content was found in the range of 92.47 ± 2.25 to 99.89 ± 0.58 % in Hydrochloric Acid (pH 1.2). % yield was within 100% to 101% indicating the acceptability of method for preparation of solid dispersions. Low values of standard deviation of drug content in SDs indicates uniform drug distribution in all the prepared batches. The values are given in Table-1.

***In-vitro* Drug Release:**

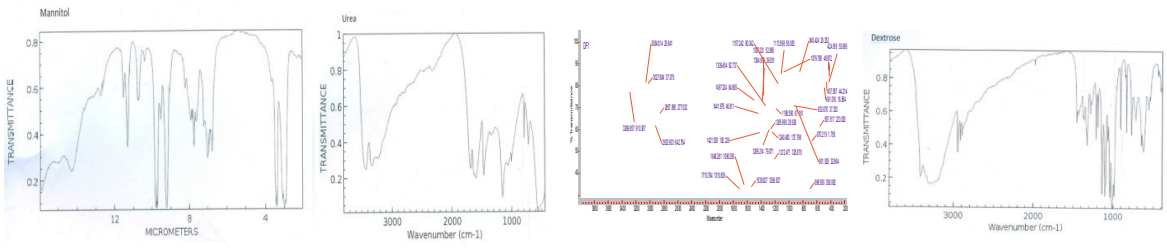
The release of the drug from all the solid dispersions was increased significantly ($p<0.05$) than from pure drug alone as indicated by value of $T_{80\%}$ in Table-1. As shown in Figures 4 to 6, the release of drug from the solid dispersions prepared with Dextrose in the ratio of 1:3 by Kneading Method was quickest in comparison to other Solid Dispersions. Values of $T_{80\%}$ are shown in Table-1. The dissolution profiles of Nateglinide – Urea, Dextrose and Mannitoal solid dispersions (SDs) prepared using different methods were compared with drug itself Figures 4 to 6. All the prepared SD systems showed a remarked enhancement of the in-vitro drug dissolution rate. In particular, SD systems prepared by Kneading method in ratio 1:3 by using Dextrose was able to produce 98 % of the drug in solution within 20min with 0.1N Hydrochloric Acid. Similarly, Drug with dextrose by Solvent Evaporation Method was able to produce about 92 % in 27min in 0.1N Hydrochloric Acid. The drug with Dextrose by Co-grinding method was able to produce about 85% of the drug within 36min in 0.1N Hydrochloric Acid.

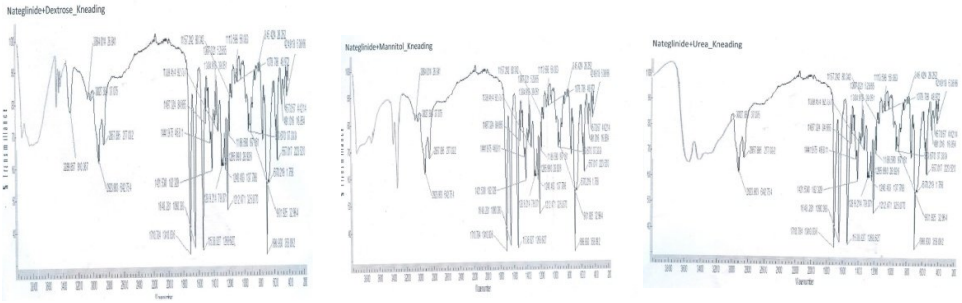
Table-1: Drug Content and *In-Vitro* Release Studies of Nateglinide and its solid dispersion in Hydrochloric Buffer pH 1.2.

S.no	Formulation code	Drug Content (% w/w) (± SD, n =4)	*In-vitro* Release in Hcl pH 1.2
		HCL pH 1.2	$T_{80\%}$ (min) (± SD) n=4
1	Pure Drug	23.56(0.47)	23 ± 0.11
2	NUK_1	96.72(1.46)	42 ± 0.21
3	NUK_2	98.43(1.87)	38 ± 0.21
4	NUK_3	96.69(1.11)	36 ± 0.91
5	NDK_1	98.72(1.44)	32 ± 0.61
6	NDK_2	98.16(1.39)	26 ± 0.15
7	NDK_3	99.89(0.58)	20 ± 0.43
8	NMK_1	96.84(2.49)	36 ± 0.21
9	NMK_2	97.50(2.90)	28 ± 0.34
10	NMK_3	96.90(0.99)	22 ± 0.56
11	NUS_1	95.14(2.24)	40 ± 0.67
12	NUS_2	95.44(1.12)	3 ± 0.78
13	NUS_3	96.07(1.71)	34 ± 0.98
14	NDS_1	98.66(1.56)	35 ± 0.54
15	NDS_2	99.62(1.56)	31 ± 0.43
16	NDS_3	95.35(1.27)	27 ± 0.32
17	NMS_1	97.45(1.74)	35 ± 0.56
18	NMS_2	98.65(1.99)	31 ± 0.67
19	NMS_3	94.81(0.37)	29 ± 0.76
20	NUC_1	96.85(0.43)	45 ± 0.91
21	NUC_2	95.85(0.86)	43 ± 0.61
22	NUC_3	94.34(1.54)	40 ± 0.67
23	NDC_1	96.44(1.55)	39 ± 0.76
24	NDC_2	98.97(1.53)	37 ± 0.43
25	NDC_3	90.46(2.69)	36 ± 0.32
26	NMC_1	92.47(2.25)	39 ± 0.78
27	NMC_2	98.43(1.87)	36 ± 0.98
28	NMC_3	96.69(1.11)	33 ± 0.21

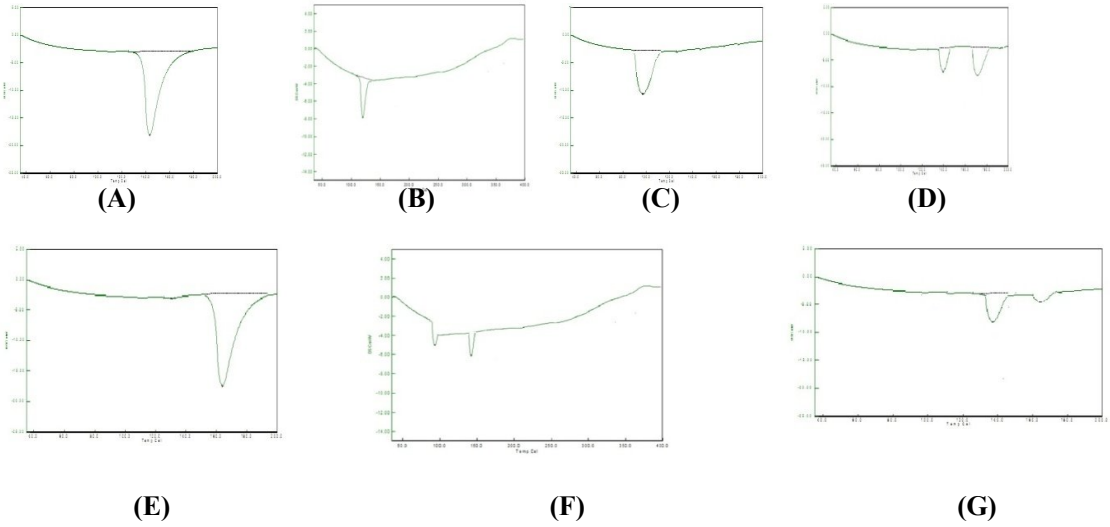
Table-2: Solubility Analysis of Nateglinide in Various Solvents.

S.no	Solution System	Solubility (µg/ml)
1	Distilled Water	30
2	2% SLS	35
3	0.1N HCl (pH 1.2)	98
4	Phosphate Buffer (pH 7.4)	42





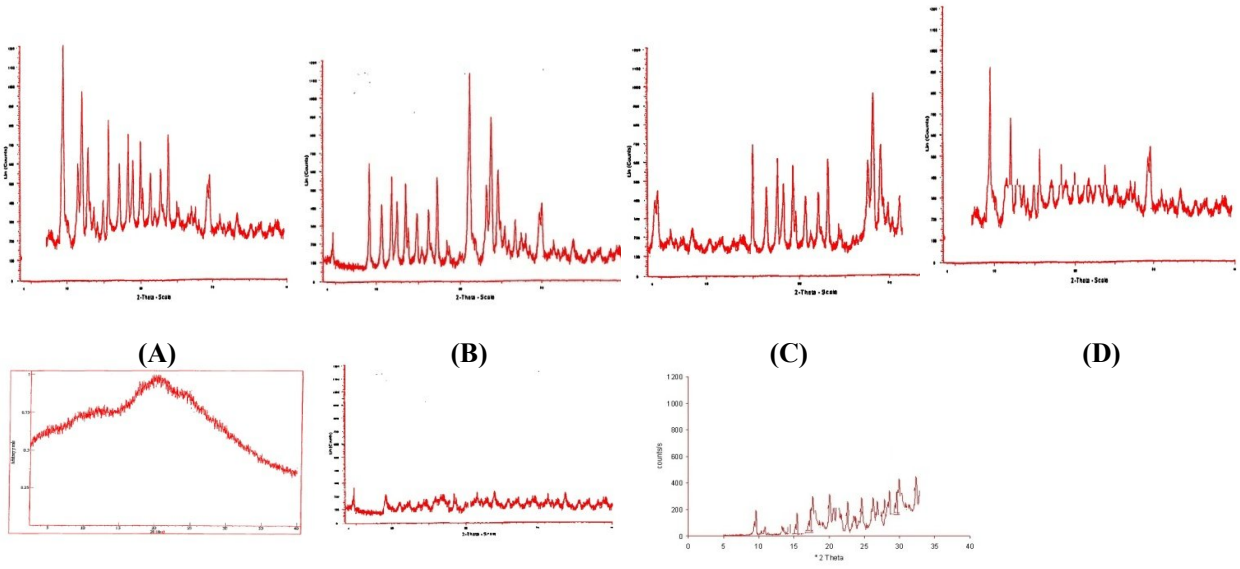
Figures -1: FTIR Studies of Pure Drug, Inert Hydrophilic Carrier, Solid Dispersions.



(A) (B) (C) (D)

(E) (F) (G)

Figures -2 : DSC Thermograms of Drug(A) , Excipients (B-Urea, C-Mannitol, D-Dextrose along with Solid Dispersion Formulations



(A) (B) (C) (D)

(E) (F) (G)

Figures -3: XRD of Drug(A) , Excipients (B-Dextrose, C-Mannitol, D-Urea along with Solid Dispersion

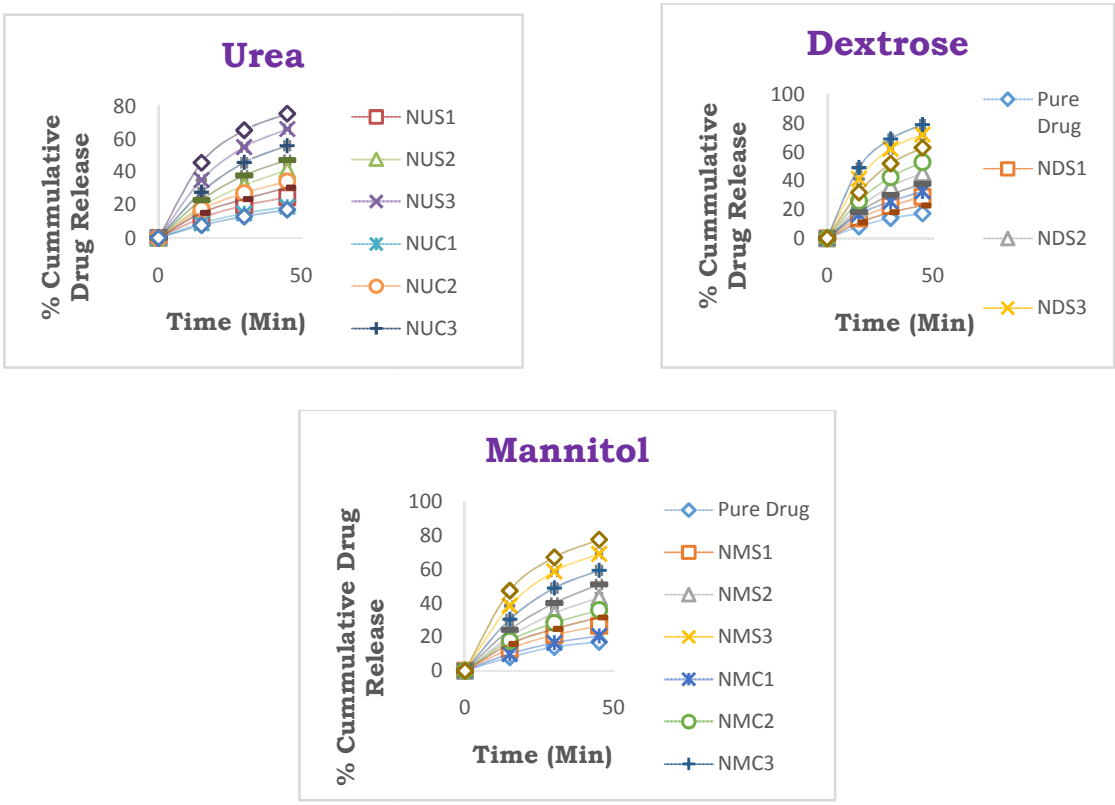


Fig-4, 5 & 6: ***In-Vitro*** **drug release of Nateglinide using Urea, Dextrose and Mannitol in Hcl Buffer pH 1.2 by Kneading Method, Solvent Evaporation Method & Co-grinding Method.**

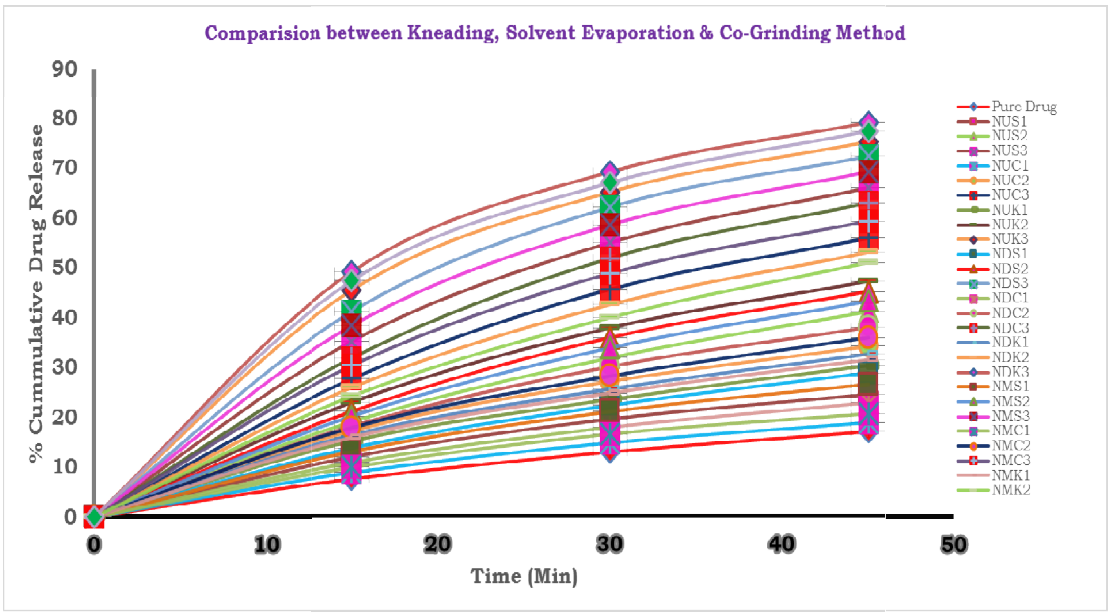


Fig – 7: Comparative Drug Release Profile of Nateglinide using Urea, Dextrose and Mannitol in Hydrochloric Acid Buffer pH 1.2.

An increase in Nateglinide dissolution rate, was also achieved by the other techniques for different solid dispersion systems, but this increase was less than ratio (1:3). It was noticed that SD systems prepared by Kneading Method were capable of improving drug dissolution rate higher than those produced by Solvent Evaporation and Co-grinding Method significantly ($p< 0.01$). On the other hand, the corresponding percentage release of pure drug in 0.1N HCl was only about 38%. $T_{80\%}$ of all solid Dispersion was kept in table-1. It could be seen that, dextrose has effectively enhanced the drug dissolution and this effect depends on the ratio of the carrier used and the method of the preparation of solid dispersion. In addition figure-7, showed the comparitive dissolution behaviors of the drug from all different systems. It has shown that, the Kneading method had the priority of enhancing the dissolution rate. The enhancement of dissolution of Nateglinide from the drug carrier may be due to several factors such as lack of crystallinity, increased wettability, amorphization and dispersibility. Incorporation of drug with a hydrophilic carrier system offered an increased wetting and reduction in interfacial tension between hydrophobic drug and dissolution medium. As indicative from dissolution data of Kneading mixtures, improvement could be attributed to higher wettability and dispersibility. Wet mixing of drug with a hydrophilic carrier and grinding with Co-solvent results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media. Furthermore, kneading results in uniform distribution of drug in the polymer crust in a highly dispersed state. Thus, when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the dissolution surface available. Moreover, other factors such as absence of aggregation and/or reagglomeration phenomenon during dissolution and particle size reduction could be attributed to a better dissolution profile.

CONCLUSION:

Solid dispersion of Nateglinide in Urea, Dextrose and Mannitol could be prepared by different methods. Nateglinide solid dispersion systems prepared by Kneading Method using Dextrose in comparasion to other two techniques had showed higher solubility and dissolution rate than the drug alone. The Kneading Method had a priority to enhance the solubility and dissolution rate over the other studied methods.

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