FORMULATION AND EVALUATION OF SOLID DISPERSION OF NABUMETONE AND DEVELOPMENT OF TOPICAL DRUG DELIVERY

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ABSTRACT

Nabumetone (NBT) BCS class II drug with 750 mg dose used for the treatment of discomfort cause due to arthritis. Formation of solid dispersion of NBT with carriers like gelucire 50/13 and urea will enhance the bioavailability. Phase-solubility studies revealed AL type of curves showed that the dispersion of gelucire 50/13 or urea with NBT significantly increases solubility of drug. The dispersions of NBT with gelucire 50/13 and urea were carried out by different methods and evaluated for *in vitro* drug release, drug content, FTIR, DSC, XRD. All dispersions showed improvement in dissolution rate in comparison with pure drug. These evaluation techniques showed distinct loss of drug crystallinity and showed improvement in dissolution rate. All dispersions were found stable after stability study. Methods showing best drug release for in vitro studies were selected for further study of development and evaluation of topical gel formulation. A topical gel has been developed using carbapol 940, propylene glycol, sodium lauryl sulphate. The formulations were evaluated for the physico-chemical and release characteristics. The optimized batch of gels showed good mechanical and physicochemical properties. The results indicated that gel with good bioadhesive and permeability properties could be prepared. The *in vitro* diffusion study showed drug release with urea was 76.49% and that with GLR 50/13 was 88.46% in distilled water with solvent wetting method after 8 hrs.

KEYWORDS

Solid dispersion, Nabumetone, Gelucire 50/13, Urea and Topical gel.

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INTRODUCTION

BCS class II i.e. poorly water-soluble drugs often show low bioavailability when administered orally. The absorption of drugs in the GI tract is a rate-limiting step and this result in variations of dissolution rate and incomplete bioavailability. The challenging and important step in the process of

drug development is improvement of the dissolution rates and bioavailability of water-insoluble drugs. Chemically, Nabumetone (NBT) chemically is 4-(6-methoxy-2-napthyl) 2-butanone. It has half life of 23 hours and dose is 750 mg. It is used for the relief of pain and discomfort occurred because of arthritis. It is also for treatment in poultry suffering from leg bone joint infection and weakness. Leg weakness in poultry is the problem for industry from many years and has significant economic importance in breeding broilers, turkeys, etc. Due to leg weakness birds cannot stand or walk and leads to starvation and even death. NBT is soluble in methanol, ethanol and isopropanol. It is almost insoluble in water as reported solubility in water is less than 0.00193 mg/ml. It is necessary to improve the dissolution rate of NBT to enhance the bioavailability. There are many chemical or formulation approaches for improvement in drug dissolution and bioavailability. For improving the dissolution and bioavailability of poorly soluble drug most successful technique is solid dispersion among the various techniques. There are various methods for preparation of solid dispersion. All methods are simple, economic, and advantageous to enhance dissolution rate.

Skin is one of the most easily available routes for drug administration and main route for topical drug delivery system. Topical preparations are applied on the skin for local or systemic effects. Topical drug delivery can be defined as the application of formulations containing a drug to the skin for treatment of cutaneous disorder. Topical delivery is an attractive route for local and systemic treatment. Gels are relatively newer class of dosage forms created by entrapment of liquid in a network of colloidal particles. These particles may consist of inorganic or organic polymers of natural or synthetic origin. Appearance of gel depends upon the nature of colloidal substances and liquid in the formulation.

Topical gels are semisolid formulations consist of a high ratio of solvent/gelling agent. Gels are transparent or translucent in appearance with high degree of physical or chemical cross-linking. On dispersing gelling agent in solvent it forms colloidal network structure and limits fluid flow as solvent molecules get entrapped in the colloidal network. Gels have viscoelastic property. The matrix structure formed during storage which breaks easily on shaking or squeezing. It is easy to apply on skin as gets thinner on pressure and adhere to the skin after application. This it has better application property and stability in comparison to other topical preparation. Topical gels are intended for skin application for local action or penetration of medicament or for their emollient or protective action. The gels are non-greasy and can be washed easily.

MATERIAL AND METHODS
Materials
Nabumetone was supplied as a gift sample by Triveni Chemicals, Vapi, India. Gelucire 50/13 and urea were gifted from Analab fine chemicals, Mumbai, India. Carbapol 940, sodium lauryl sulphate, ethanol and triethanolamine were also gifted from Analab fine chemicals, Mumbai, India.
Methods
Drug Characterization
Melting point of NBT was determined by capillary method with use of melting point apparatus to assess purity of NBT. From the calibration curve of NBT on UV (Varian Carry 100, Australia), λ_{max} was selected.
Solubility
NBT solubility studies were performed by adding excess amounts of NBT in water and flasks were kept in shaker for 48 hrs. The concentrations were calculated by analyzing absorbances of solutions on UV.
Infra Red Spectroscopy
To characterize NBT, FTIR (Varian 640 IR, Australia) was used. The samples were prepared by the KBr pellet method and spectra were scanned over IR frequency range.
Phase Solubility Studies
An excess amount of NBT was added to aqueous solutions of gelucire 50/13 or urea in increasing concentration (1%, 2%, 3%, 4% and 5%w/v). The flasks were sealed and kept in mechanical shaker at $37\pm0.5°C$ for 72 hrs. Aliquots were withdrawn,

centrifuged, filtered, suitably diluted and absorbances measured on UV at 228nm. Solubilities of NBT at different concentrations of gelucire 50/13 or urea was calculated.

Preparation of SD
SDs were prepared at 1:1, 1:2, 1:3 ratios, by following methods.

Physical Mixtures (PM)
The NBT with gelucire 50/13 or urea was grinded thoroughly in a mortar, sieved.

Solvent Wetting Method (SW)
The NBT was dissolved in methanol, kept in sonicator for 15 minutes and this solution was then dropped into carriers placed in mortor and constantly stirred. The solvent was evaporated at room temperature in desiccator.

Saturation Solubility
By keeping equilibrium of an excess amount of NBT and SDs in 10 ml distilled water kept on a mechanical shaker at room temperature for 48 hrs. Then aliquots were withdrawn, centrifuged, filtered, suitably diluted and analyzed by UV at 228 nm to determine concentration of NBT.

CHARACTERIZATION OF SD
Percent Drug Content and Yield Study
The SD equivalent to 100 mg/ml of NBT was added in 5ml methanol, sonicated for 10 min., volume was adjusted suitably with distilled water. The solution was filtered, suitably diluted and assayed on UV at 228 nm. The NBT content was calculated by using calibration curve. The SD was weighed and yield was calculated by using formula as

% Yield = (a/b) X 100

'a'= practical weight of SD obtained and 'b'= theoretical weight of SD.

In Vitro Release Study
In vitro release studies of NBT from SD were studied in conditions as dissolution medium used was 900 ml distilled water, 37±0.5ºC temperature and 75 rpm. The apparatus used was USP I dissolution test apparatus, basket type (make: TDT-08L Electrolab, Mumbai, India). Samples were withdrawn at specified time interval, filtered, diluted suitably and assayed for concentration of NBT using UV at 228 nm. Experiment performed in triplicates. Dissolution profiles of SDs were analyzed by plotting graph of time versus % drug release.

Fourier Transform Infrared Spectroscopy Study (FTIR)
The spectra of NBT, carriers and SDs were scanned in the range of 4000 to 500 cm-1 and recorded with FTIR spectrophotometer using KBr pellets. The drug-carrier interactions were studied from these spectra.

Powder X-Ray Diffraction Study (PXRD)
XRD with make Philips PW 1729, Netherlands was used for analyzing XRD patterns of NBT and SDs with conditions as Ni filter, CuK radiation, 20 mA current and 0.2 inch receiving slit. The samples were analyzed in range of 5° to 50°, with 2θ scan step size of and 1 second scan step time.

Differential Scanning Calorimetry Study (DSC)
DSC (Schimadzu Corporation, Star 821 e, Switzerland) was used to analyze the curves of NBT, carriers and SDs representing the rates of heat uptake. DSC was calibrated prior to analysis using an indium standard. About 2-5mg of sample was weighed in a standard open aluminum pans with conditions as 40-250°C scanning range, 10°C/min heating rate and purged with dry nitrogen.

Stability Study of SDs
The selected SDs were packed in tightly closed bottles which were capped with aluminum. They were stored at different relative humidity (RH) levels as $25^0C/60\%$ RH, $30^0C/65\%$ RH, and $40^0C/75\%$ RH for 3 months. These SDs were evaluated for their physical changes such as color and texture, drug polymer interaction using FTIR, drug content and In vitro drug release study.

Formulation of topical gel
SD showing high solubility was selected for further development of topical gel. Gel formulations were prepared by dispersing 5% w/w Carbapol 940, 1% w/w SLS and quantity sufficient glycerin in water by continuous stirring for a period of 2 hr. NBT was dissolved in ethanol and the solution was added gently to carbapol 940, sodium lauryl sulphate, glycerin dispersion under continuous stirring. The dispersion was then allowed to hydrate and swell, adjusted the pH. The mixture was stirred gently

until homogeneous gel was formed. All the samples were allowed to equilibrate for at least 24 hrs at room temperature.

EVALUATION OF TOPICAL GEL
Physical Evaluation
Prepared and optimized batches of topical gel were evaluated by sensory evaluation for clarity, colour, homogeneity, presence of particles and fibres.

Spreadability
Spreadability was determined by an apparatus introduced by Mutimer *et al*. The apparatus consists of a wooden block provided by a pulley at one end and glass plate was fixed on the block. An excess of gel (about 2 gm) under study was placed on the lower plate. To expel air between two plates and to provide a uniform film weight was placed on the plates. The upper plate was then subjected to a pull and noted the time (in sec) required by the upper plate to cover a distance of 10 cm. A shorter the time interval better the spreadability.

Measurement of pH
The pH of the optimized gel formulation was determined with a digital pH meter at room temperature. The calibration of pH meter was done by using standard buffer solution pH 4, 7 and 9.2. The gel (2.5 gm) was dispersed in 25 ml of purified water. Then pH meter was dipped in the gel solution and the pH was recorded.

Viscosity
The viscosities of optimized batches were determined using Brookfield's viscometer. The gel was placed in the sample holder and the suitable spindle (No.7) was lowered perpendicularly into the sample. The spindle was allowed to rotate at a constant optimum speed. The viscosity of the formulation was recorded at room temp.

Extrudability
Extrudability was based upon the % quantity of gel extruded from tube on application of certain load. The formulation under study was filled in a clean, aluminum collapsible one-ounce tube with a nasal tip. It was then placed in between two glass slides and was clamped. When constant load was placed on slides, gel got extruded through the tip and extrudability was determined by weighing the gels.

% Drug content
Accurately weighed 0.5 gm of gel (equivalent to 10 mg of NBT) was transferred in 100 ml of volumetric flask, diluted with ethanol and sonicated. Then this solution was suitably diluted and absorbance was measured using UV against blank at 228 nm and drug content was determined.

DRUG RELEASE STUDY
In-vitro diffusion study: Cellophane membrane
A modified Franz diffusion cell was used for permeation studies. Cellophane membrane (no. 10, pore size 2.4 nm) soaked in phosphate buffer pH 6.8 for 24 hours before use. Cellophane membrane was placed in between donor and receptor compartment. Accurately weighed 1gm of gel was transferred to donor compartment and 25 ml of phosphate buffer pH 6.8 was filled in receptor compartment. The cell was agitated by a magnetic stirrer at 50 rpm at $37\pm1°C$. Aliquots were withdrawn at specific interval of time and replaced with equal volume of fresh phosphate buffer pH 6.8. The samples were diluted suitably and absorbance was measured at 228 nm.

Ex-vivo diffusion study: Goat skin
Tissue Preparation
The skin of male goat, free from any visible disease was obtained immediately after sacrifice from a local slaughter house. It is transported to the laboratory in isotonic phosphate buffer (pH 6.8) and opened longitudinally and rinsed with same. Dorsal hairs and adhering subcutaneous fat was removed carefully. The excised skin was immersed in isotonic saline at 60^0C for 1min and ready for diffusion study. Phosphate buffer solution with pH 6.8 and maintained at 37 ± 0.5^0C kept in receptor compartment. 1 gm gel was placed in donor compartment, spreaded evenly and the permeation study was similarly carried out as that with cellophane membrane.

RESULTS AND DISCUSSION
Drug Characterization
Melting point of NBT was found in the range of 80^0C- 82^0C.

UV Spectroscopic Study
The maximum absorbance of NBT found at 228nm. So, λ max of NBT selected at 228nm shown in Figure No.1.

Stability in Solvents
When NBT was analyzed in water, 0.1 N HCl and phosphate buffer with pH 6.8, no major changes observed. This indicated that NBT stable in these solvents.

Infra Red Spectroscopy
In the FTIR spectra analysis the characteristic peaks of NBT were observed at wave numbers 3062.25, 2956.83, 2848.37, 2812.19, 1705.04, 1634.02, 1485.64, 1387, 1363.54, 1208.25, 957, 895 and 845 cm^{-1} for specific structural groups, confirming the purity of drug.

Phase Solubility Study
This study showed that the curve (Figure No.2) obtained are A_L type because of linear increase in solubility as the value of R^2 closed to 1. The solubility parameters of NBT at 25ºC are 0.0136 was slope, 0.9976 was R^2. The results of saturation solubility study (Table No.1) indicated that maximum increase in solubility with 1:3. The solvent wetting method showed maximum saturation solubility.

Saturation solubility

Percent Practical Yield and Drug Content
The results for practical yield and drug content were summarized in Table No.2.

***In Vitro* Release Study**
The in-vitro release of SDs showed significant increase in drug release, in comparison with pure crystalline NBT in dissolution medium. Among two methods, the maximum of dissolution enhancement was found with solvent wetting method.

FTIR
Figure No.3 showed some additional peaks in IR spectra which may be due to the carriers. While all other characteristic peaks of NBT are at the same wave number. IR spectra indicated that there were no interactions of drug with carrier.

PXRD
Figure No.4 showed crystalline nature which was indicated by the numerous distinctive peaks at 2θ values are 19.26 and 26.50 in PXRD study of NBT.

There were no numerous distinctive peaks seen in XRD pattern of SD. This showed that the high amount of NBT was dissolved in carrier in amorphous nature.

DSC
The DSC curve of NBT exhibited a sharp endothermic peak at 83.73°C due to fusion. Analogously, the thermal curve of GLR 50/13 showed a single endothermic effect with a peak near about at 57.00 ºC, corresponding to its melting point. The DSC graph of SDs showed position of endothermic peak is shifted at 78.11 ºC (Ratio 1:1) and 75.17 ºC (Ratio 1:2) and 60.60 ºC (Ratio 1:3) respectively with decreased intensity than pure NBT. It indicates that crystalline nature of NBT gets transformed into amorphous carriers and thus melting of NBT became faster. The thermo grams showed in Figure No.5.

Dissolution Study
Dissolution study was performed with both the methods of preparation of solid dispersion by using different ratios, which was finalized after preliminary saturation solubility study, viz. 1:3. The release for cumulative % drug release obtained for all the formulations and pure NBT are tabulated. Figure 6 shows graphical presentation of drug release study. The dissolution rate of pure NBT was very poor and after 2 hrs i.e. 10.21 ± 1.39 %. While the dissolution rate of SDs after 2 hrs for SD of NBT: GLR 50/13 (SW) with ratio 1:3 showed maximum drug release i.e.26.17 ± 1.68 and that for SD of NBT: Urea (SW) with ratio 1:3 was found to be 35.49 ± 0.41.

Stability Study of SD
The stability study was carried out for SD prepared by PM and SW methods and parameters for study were drug content, in vitro release studies and FTIR. There was no degradation observed in stability studies. Thus, prepared SDs can be stored for one year.

Evaluation of Topical Gel
From the study of dissolution profile of all SDs the F3 and F6 batches were selected for further study as drug release of SW method with drug to carrier ratio 1:3 showed good release compared to another method with other ratios.

Physical Evaluation

The prepared gel formulations were examined visually for color and appearance. All formulations were clear. All batches of gel formulations showed good homogeneity with absence of lumps.

Spreadability

The value of Spreadability indicates the degree of shear required to apply the gel. Table No.3 showed spreadability values for selected formulation batch.

Measurement of pH

The pH of formulations was in range of 6.91 ± 0.64 to 7.2 ± 0.36 which lies in the normal pH range of skin. Table No.4 summarizes results of pH measurement.

Viscosity

Viscosity of gel measured at 2, 4, 10 and 20 rpm and summarized in Table No.5. Viscosities were proportional to the concentration of gelling agent. As rotating speed increased, the viscosity decreased which indicated shear thinning property.

Extrudability

Extrudability of all the formulations is higher than 80%. All the formulations showed good acceptance properties. Results are shown in Table No.6.

Drug content

The drug content of both formulations was in the range of 88.90 ± 1.77 % to 94.68 ± 2.31 %. The results summarized in Table No.7, showed uniform distribution of drug throughout the gel.

IN-VITRO DRUG DIFFUSION STUDY
Cellophane membrane

The graphical presentation shows in Figure No.7 and 8. SDs which showed maximum drug release in distilled water was selected for further preparation and diffusion study of gel. Formulation batch F3 and F6 showed good release profile due to the lower concentration of HPMC K4M and higher concentration of Carbopol 940. As there is increase in concentration of gelling agent leads to decreased drug release from formulations due to increase in viscosity of formulation.

Ex-vivo drug permeation study

Ex-vivo study was done with only two best optimized formulations i.e. F3 and F6. It was found that ex-vivo release was less than in-vitro release through both membranes. This decrease in drug release may be due to the fat content and thickness of Goat skin. Figure No.9 and 10 show graphical presentation of release profile.

Table No.1: Saturation solubility study

S.No	Saturation solubility on various ratios	Preparation Methods for carriers			
		Physical mixture (PM)		Solvent wetting (SW)	
		GLR 50/13	Urea	GLR 50/13	Urea
1	1:1	48.97 ± 0.91	57.41 ± 1.74	61.55 ± 1.56	69.89 ± 0.41
2	1:2	52.38 ± 2.48	66.65 ± 1.86	65.82 ± 1.42	74.56 ± 0.93
3	1:3	57.14 ± 1.68	73.91 ± 0.93	73.49 ± 0.95	81.38 ± 1.24

Table No.2: Percent Practical Yield and Drug Content

S.No	Preparation methods	Practical yield ±SD*(%)		Drug content ±SD*(%)	
		GLR 50/13	Urea	GLR 50/13	Urea
1	Physical mixture (PM)	73.34 ± 0.93	84.83 ± 1.32	71.90 ± 0.98	81.24 ± 1.30
2	Solvent wetting (SW)	79.86 ± 0.54	91.59 ± 1.56	75.34 ± 1.73	86.04 ± 1.08

Table No.3: Spreadability of the formulated gel batches

S.No	Formulation batch	Spreadability (g.cm/sec)
1	Pure drug	20.65 ± 1.43
2	F3	22.85 ± 2.31
3	F6	27.61 ± 1.24

Table No.4: pH measurement of formulated gel batches

S. No	Formulation Batch	pH
1	Pure drug	7.14 ± 0.92
2	F3	6.91 ± 0.64
3	F6	7.20 ± 0.36

Table No.5: Viscosity of Finalized SD Batches at Various RPM with GLR 50/13 and Urea

S.No	Batches	2 RPM	4 RPM	10 RPM	20 RPM
1	Pure Drug	12000 cps	6800 cps	5400 cps	4000 cps
2	F3	16000 cps	13600 cps	9300 cps	7100 cps
3	F6	20000 cps	14200 cps	11500 cps	8000 cps

Table No.6: Extrudability of gel formulation batches

S.No	Batches	Weight of gel in tube(gm)	Weight of gel Extruded	Extruded amount (%)
1	Pure drug	10.41	8.92	84.86
2	1	9.86	8.32	85.14
3	2	10.28	8.64	88.59

Table No.7: Drug content of formulated gel batches

S.No	Formulation batches	% drug content
1	Pure drug	82.56 ± 2.40
2	F3	88.90 ± 1.77
3	F6	94.68 ± 2.31
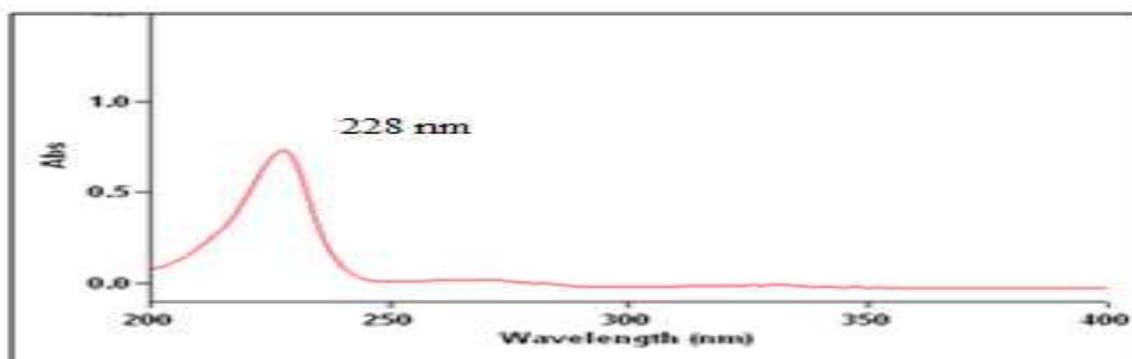
Figure No. 1: UV Spectroscopic Study of NBT (g/ml)
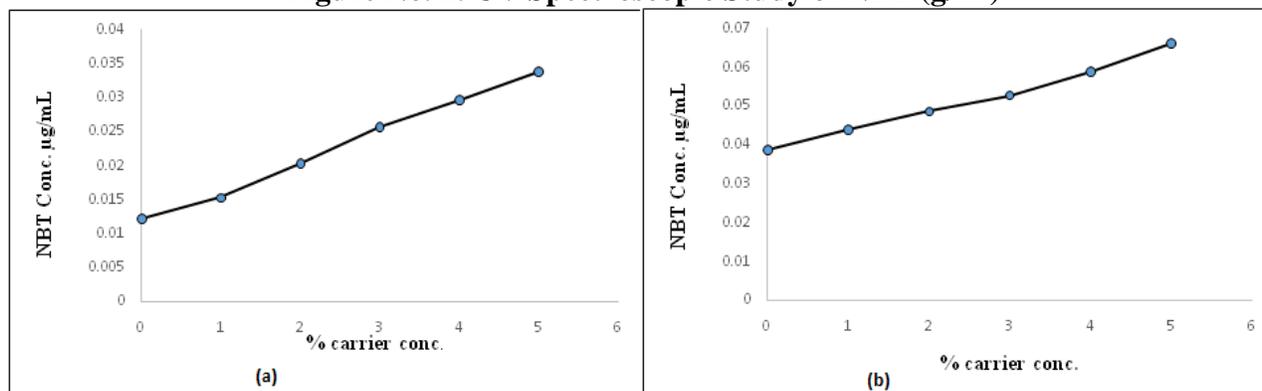
Figure No.2: Phase Solubility study in aqueous solutions: (a) NBT with GLR 50/13 and (b) NBT with urea
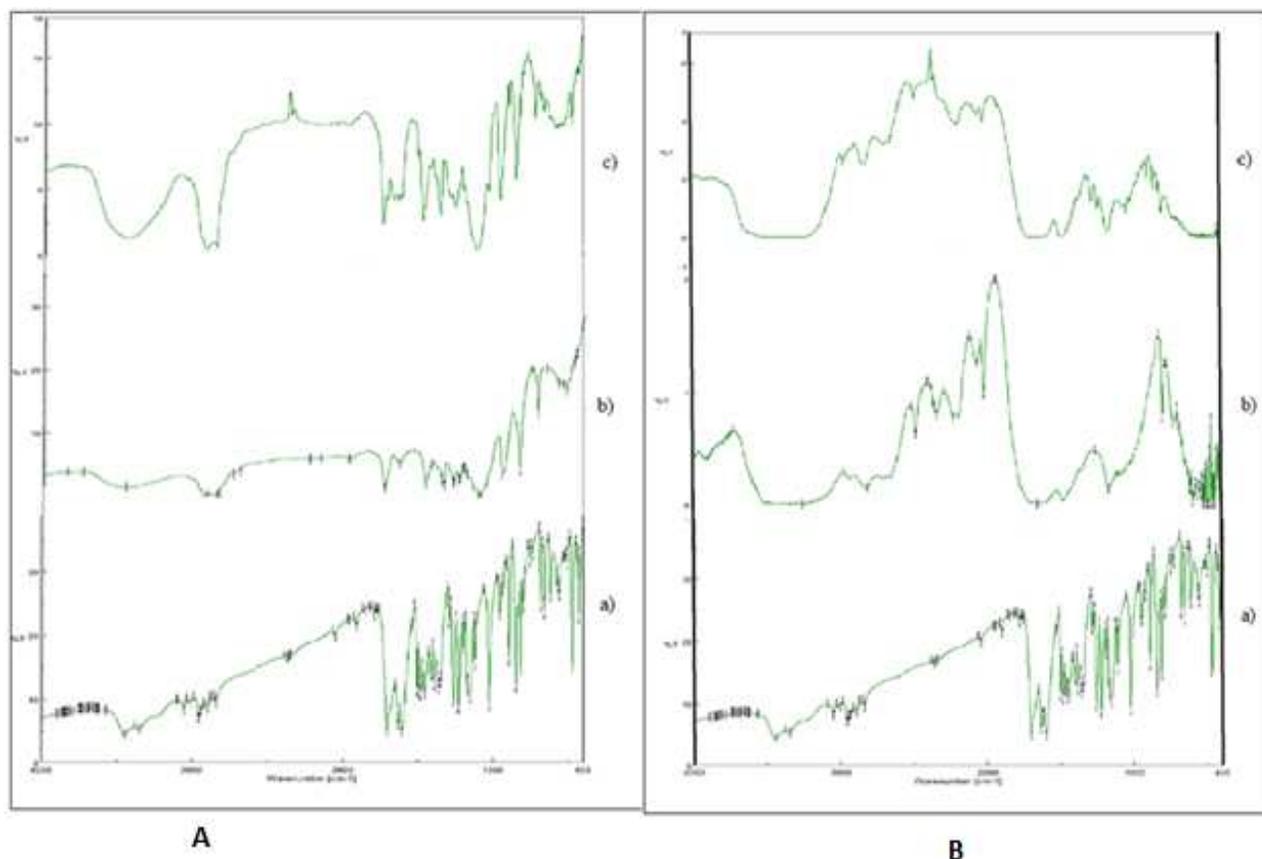
Figure No.3: FTIR spectra A: a) NBT, b) GLR 50/13 and c) NBT:GEL 50/13 (1:3) SW
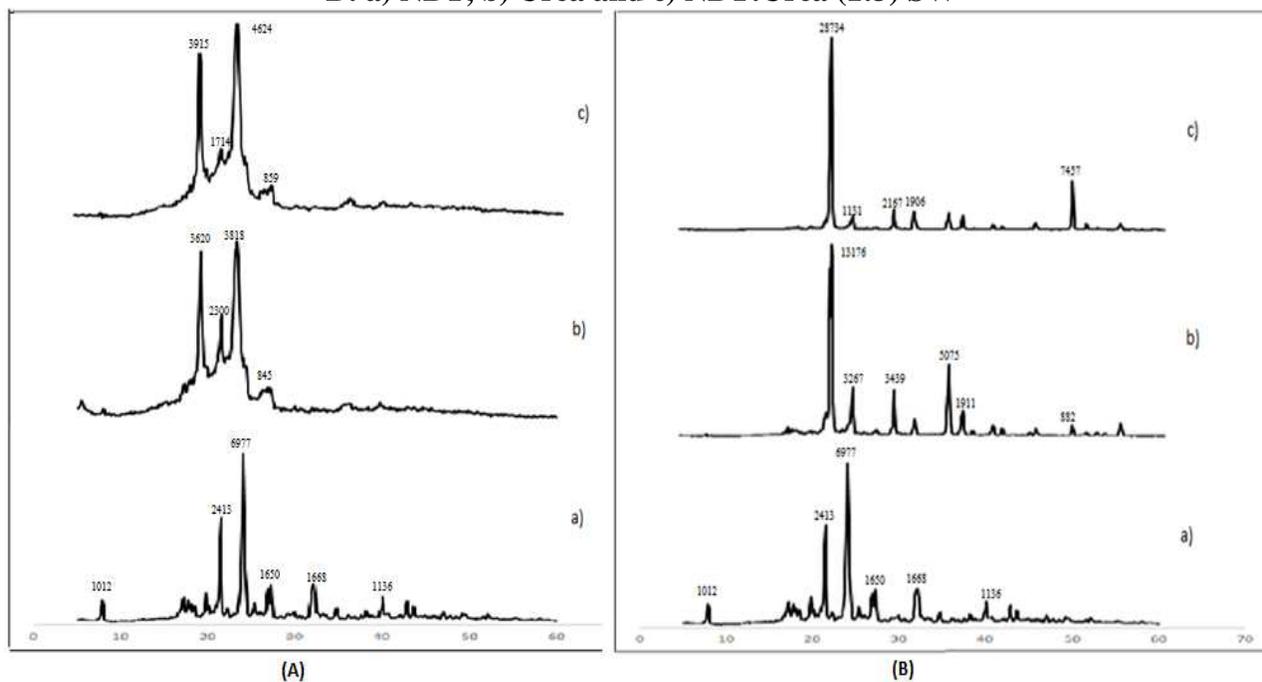**B: a) NBT, b) Urea and c) NBT:Urea (1:3) SW**

Figure No.4: PXRD pattern (A): For NBT: GLR 50/13 ratio 1:3 - a) NBT, b) SW, c) PM and (B): For NBT: Urea ratio 1:3 - a) NBT, b) SW and c) PM
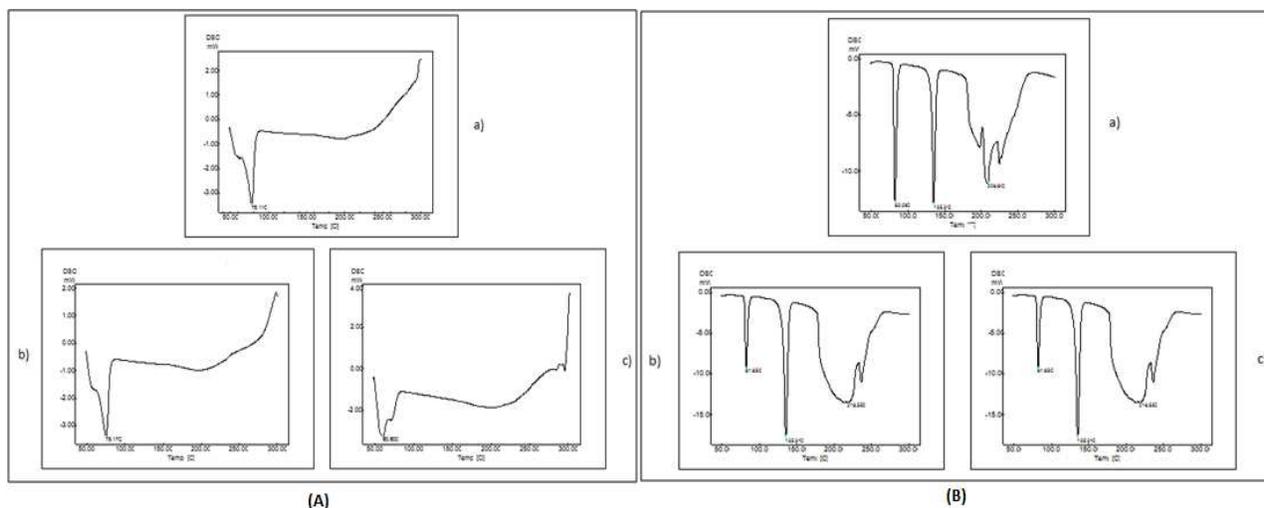
Figure No.5: DSC thermo grams of SD of NBT (A): with GLR 50/13 in ratios a) 1:1, b) 1:2 and c) 1:3, (B): with urea in ratios a) 1:1, b) 1:2 and c) 1:3
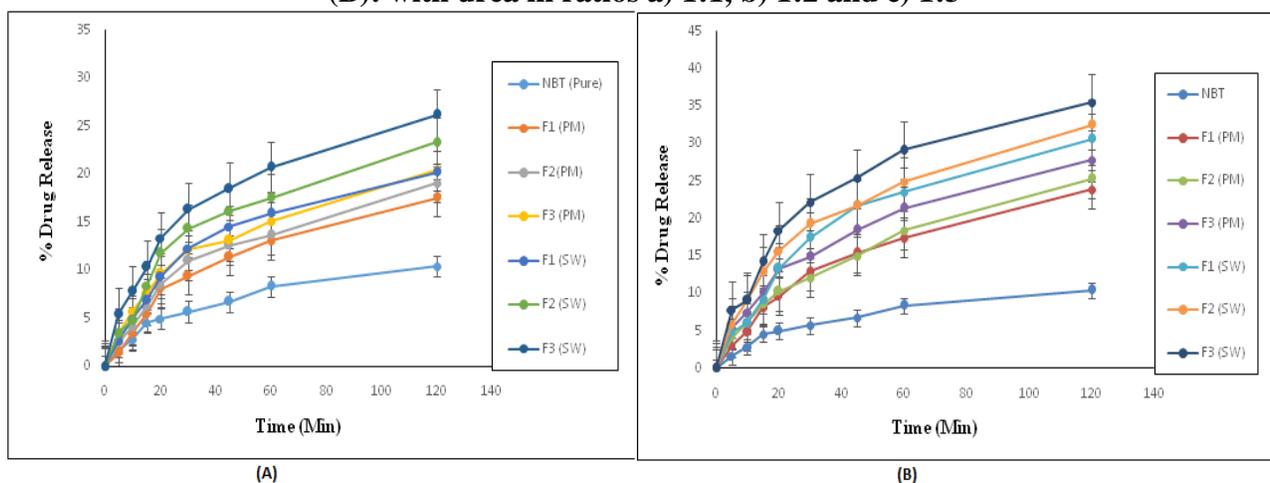

Figure No.6: % Drug release profile of all ratios in distilled water (A): NBT PM and SW with GLR 50/13 and (B): NBT PM and SW with urea
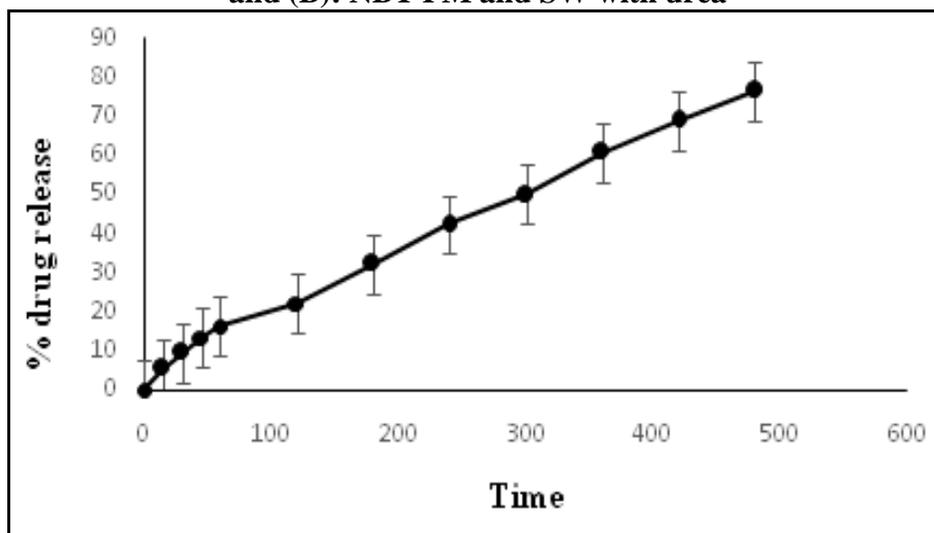
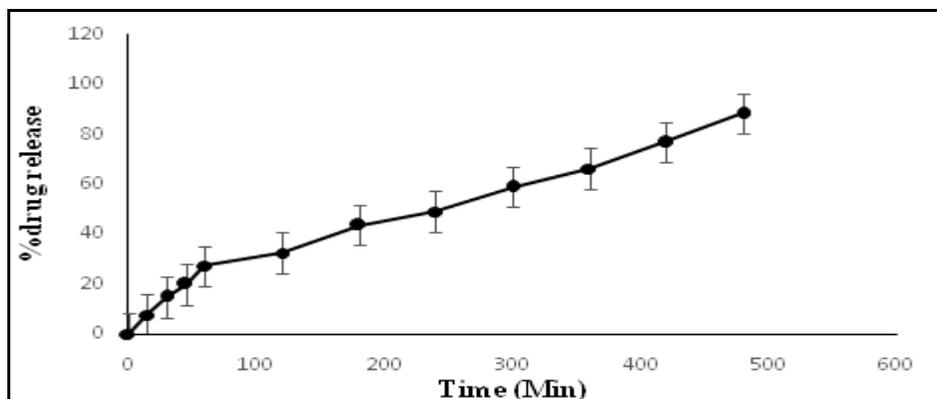**Figure No.7: Diffusion Study (Cellophane Membrane) NBT+ GLR 50/13 (ratio 1:3) F3 batch**

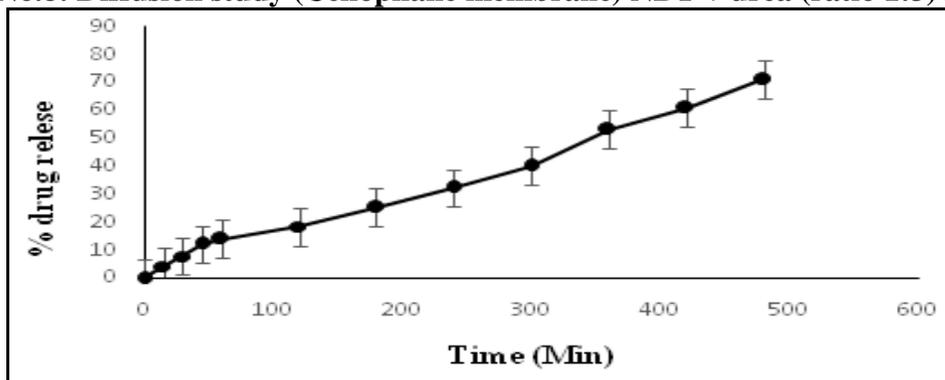**Figure No.8: Diffusion study (Cellophane membrane) NBT + urea (ratio 1:3) F6 Batch**

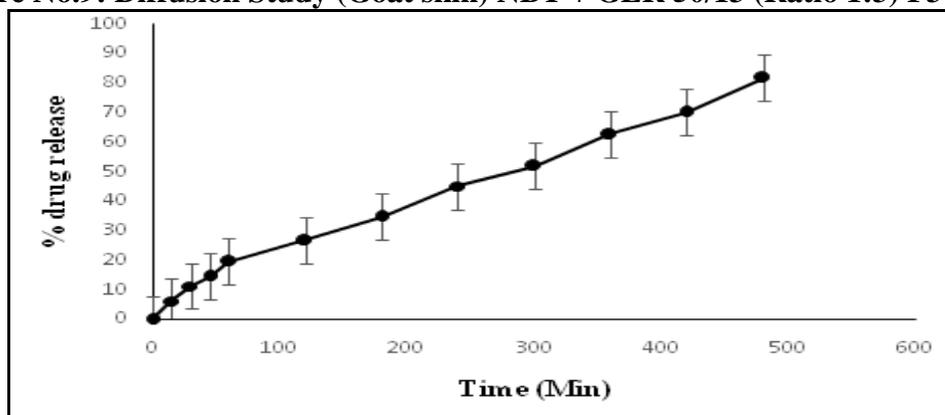**Figure No.9: Diffusion Study (Goat skin) NBT + GLR 50/13 (Ratio 1:3) F3 Batch**

Figure No.10: Diffusion Study (Goat skin) NBT + Urea (Ratio 1:3) F6 Batch

CONCLUSION
The solid dispersion obtained by solvent wetting method provides better control of drug release rate than physical mixture for same drug to polymer ratio. The water-soluble carrier gelucire 50/13 and urea and different techniques were studied to formulate solid dispersion, which gives improvement in solubility and drug release profile of nabumetone. The DSC, XRD and FTIR study had shown no interaction between nabumetone and carriers i.e. gelucire 50/13 and urea. The dispersion system is more efficient for preparation of nabumetone sustained-release mucoadhesive buccal patches which can reduce first pass metabolism of the drug with improved dissolution.

CONFLICT OF INTEREST
We declare that we have no conflict of interest.

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