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Development and Evaluation of Polyvinyl Alcohol Gel of Indomethacin by Nanosuspension and B-Cyclodextrin Technique

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ABSTRACT

Indomethacin from a class of NSAID drugs used to relieve pain, swelling, and joint stiffness. It is a class II drugs which have low water solubility. This study was aimed to investigate the solubility and permeability of Indomethacin in two different techniques such as nanosuspension and β-cyclodextrin. Nanosuspension are submicron colloidal dispersions that increase dissolution rate and diffusion of drug into the skin. B-cyclodextrin is a hydrophobic interior and hydrophilic exterior, complexes formed with hydrophobic compounds. To compare the solubility and permeability of the different gels. Two gels were formulated in a different way, for nanosuspension Indomethacin was dissolved in ethyl acetate and the solution was heated to 80 ^{0}C and allowed to evaporate. β-cyclodextrin was prepared by kneading technique 2:1 (β-CD: Indomethacin) molar ratio. Wetted with drops of methanol and allowed to dry. The gels were kept in cold room to maintain its stability. The formulated gels were evaluated for various physio-chemical evaluation tests such as solubility studies, pH, Franz diffusion and physiochemical evaluation. All other basic materials needed for gel preparation were used. The gel formulated in β-cyclodextrin showed a higher solubility (0.999) absorbance than nanosuspension (0.437) but nanosuspension showed a higher permeability in releasing the drug over 6 hours (23.13%) but in the same duration B – cyclodextrin releases 9.38% of Indomethacin across the membrane.β-cyclodextrin is more soluble in water whereas nanosuspension has a higher permeability that diffuse across the membrane. nanosuspension formulation proved to have a higher pharmacological effect.

Keywords:
Nanosuspension, B-cyclodextrin, solubility, permeability, Indomethacin

Introduction

Indomethacin form a NSAID's class was used as a model for low water solubility in this research study. Solubility is a property of matter such as solid, liquid and gas that the substance solubility is measure on the extent of saturation, as adding more solutes the solute did not dissolve but forms a precipitate. According to Biopharmaceutics Classification system Indomethacin is Class II drug with low water solubility and high permeability. Indomethacin is used as pain reliever, reduce the swelling and joint stiffness. Poorly soluble drugs tend to be eliminated in the gastrointestinal tract before they are completely dissolved and goes to the circulation lead to a lower bioavailability of drug (Kumar *et al.,* 2011). According to yadavsk, nanosuspension is defined as a fine colloid biphasic, dispersed particle in an aqueous medium with the size below 1µm. This method is used to enhance the solubility of the poorly water-soluble drugs as well as lipid media. The reduced particle size with a high surface area increases the solubility and the rate flooding of the active compounds. Apart from these advantages the suspension has also advantages for the liquid formulations than the others. The next modification is an inclusion complex by taking up the drug molecule or the lipophilic structure of the molecule into the central cavity which is polar cyclodextrin occupied by water molecules. This technique has many advantages such as increasing the solubility, improving the stability, minimising the side effects and a good improvement in the bioavailability (Chaudhary& Patel, 2013).

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MATERIALS AND METHODS

The aim of this study is to improve the solubility of Indomethacin by nanosuspension and B-cyclodextrin technique and to identify the best technique that has a high solubility and a greater permeability.

Materials

Materials	Uses
Indomethacin	Active ingredient
B-Cyclodextrin	Solubilizing agents
Methanol	solvent
Polysorbate 80	solvent
Acetyl acetate	solvent
Triethanolamine	Surfactants
Cellulose nitrate membrane	Filtration and clarification
Isopropyl myristate	An emollient, thickening agent
Tri CL buffer powder	PH

Gel formulation

Table 1: Formulations (1% of Indomethacin gel)

Ingredients (% w/w)	Formulation		
	Gel A	Gel B	Gel C
	Plain Indomethacin + PVA gel	B-CD inclusion complex of Indomethacin + PVA gel	Nano-suspension Indomethacin + PVA gel
Indomethacin	1	1	1
PVA powder	2.5	2.5	2.5
Glycerol 85%	10	10	10
Nipagin	0.1	0.1	0.1
Nipazol	0.01	0.01	0.01
Water up to	100 mL	100 mL	100 mL

Preparation of pure gel

10g of PVA powder was sprinkled gently on a beaker containing warm water. It was then stirred magnetically using the magnetic stirrer. A small amount of cold water was added to the beaker and mixed well and kept overnight for complete gel dispersion. By kneading technique 10g of the pure gel was mixed with the plain Indomethacin (Nagpal*et al.*, 2019).

Preparation of nanosuspension gel

Indomethacin was dissolved in ethyl acetate and stabilizing surfactant, polysorbate 80 was added to distilled water and solution was heated to 80^0C to 85^0C. Indomethacin in ethyl acetate was

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transferred to distilled water drop wise via syringe and mixture was continuously stirred magnetically. Ethyl acetate was allowed to evaporate and nanosuspension formed. The PVA powder was sprinkled gently in beaker containing nanosuspension of Indomethacin at 65 to 70^{0}C. Then it was magnetically stirred at high speed until smooth homogenous gel is formed (Shen*et al.*, 2018).

Preparation of inclusion complex

B-CD inclusion complex of Indomethacin was prepared in molar ratio of 2:1 (β-CD: Indomethacin) by kneading technique. β-CD was placed in mortar and wetted with few drops of 1:1 mixture of methanol water and kneaded with Indomethacin by geometry mixing to obtain a mass with pasty consistency. Mixture was allowed to dry, and inclusion complex formed. 10g of the pure gel was mixed by kneading technique (Sauceau*et al.*, 2008).

RESULT

a) Physiochemical evaluation

Table 2: Physical appearance of formulations

Formulation	**Color**	**Texture**
Plain gel	Transparent	Gel like
Nanosuspension	Light yellowish	Gel like
B-cyclodextrin	Whitish	Less gel creamy

pH measurement by using electrometric method

Table 3: The pH reading of formulations

Formulation	**Reading 1**	**Reading 2**	**Reading 3**	**pH reading**
Plain gel	6.98	7.00	7.01	7.09 ± 0.02
Nanosuspension technique	6.88	7.23	7.06	7.03 ± 0.01
B-Cyclodextrin	6.76	6.88	6.80	6.81 ± 0.02

Solubility studies

Table 4: UV Absorbance

Formulation	**Reading 1**	**Reading 2**	**Reading 3**	**UV-VIS Absorbance (mean)**
Plain gel	0.304	0.325	0.313	0.314
Nanosuspension	0.396	0.486	0.429	0.437
B-Cyclodextrin	0.864	0.975	1.158	0.999

Based on the UV absorbance, B-cyclodextrin has the highest reading indicating a high solubility compared to nanosuspension and B-Cyclodextrin. The data was analysed using SPSS One Way ANOVA. The difference is significant p values is less than 0.05

Franz Diffusion (Nanosuspension)

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Table 5: The mean drug release from UV-VIS

Sample/ Drug release	Reading 1	Reading 2	Reading 3	Mean	(%) Drug release
30 min	0.96	0.81	0.687	0.68	2.56
1 hour	1.42	1.44	1.28	1.18	5.7
2 hours	2.01	1.93	2.17	1.68	8.86
4 hours	2.5	2.88	2.64	2.21	12.21
5 hours	3.53	4.23	4.87	3.66	21.36
6 hours	4.781	4.76	4.33	3.94	23.13

Franz diffusion (Cyclodextrin)

Table 6: The mean drug release from the B-Cyclodextrin

Sample/ Drug release	Reading 1	Reading 2	Reading 3	Mean	% of drug release
30 min	0.51	0.55	0.533	0.531	1.60
1 hour	0.75	0.82	0.59	0.72	2.79
2 hours	0.86	0.94	1.23	1.01	4.63
4 hours	0.95	1.11	1.37	1.14	5.47
5 hours	1.74	1.88	1.31	1.64	8.63
6 hours	1.63	1.89	1.77	1.76	9.38

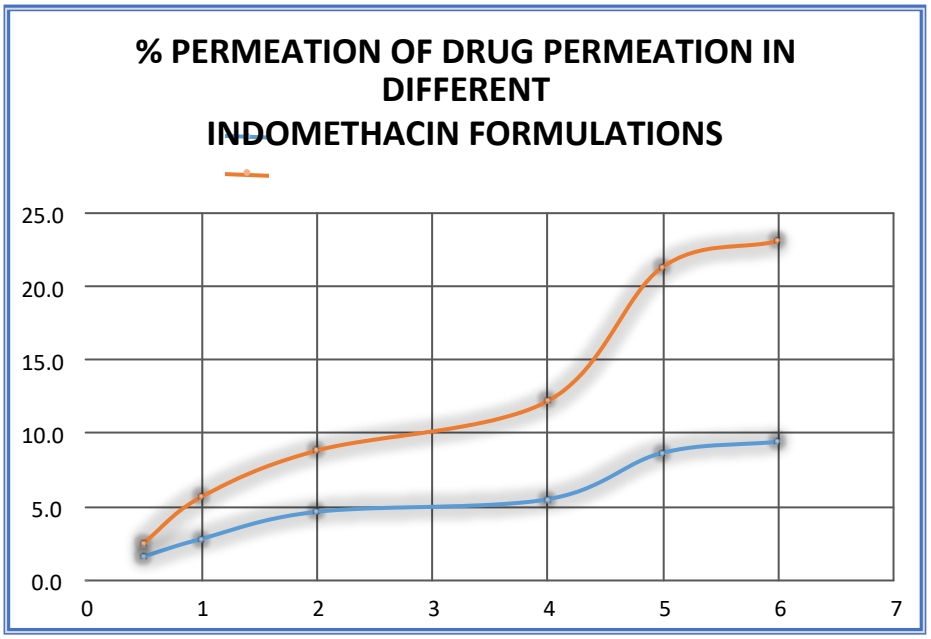

Figure 1: Comparison between the nanosuspension and B-Cyclodextrin gel

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Percentage of drug permeated from the gel shows that nanosuspension releases T23.13% of drug whereas the B-cyclodextrin drug release was only 9.38%. The in vitro permeation studies results was analysed using the student t-test (Iraji*et al.,* 2007). The p-value obtained shows that it is less than 0.05. Therefore, there is a significant difference between the drug release of the nanosuspension and B-cyclodextrin technique. Nanosuspension showed a highest permeability than B-cyclodextrin.

DISCUSSION

The different formulations of gels was observed based on the colour and texture of the gels. All the formulations have the gelly like structure because of the gelling agent. Nanosuspension is slightly yellowish because of the solvent acetyl acetate. B- Cyclodextrin is whitish colour because of the B-Cyclodextrin powder. The gel was kept in the cold room and observed for any colour change or precipitation of the drugs (Misal*et al.,* 2012). The data obtained from the solubility studies shows that B-cyclodextrin has the highest absorbance. UV-Vis light is passed through a sample and the transmittance of light by a sample is measured. More amount of drug has solubilize in Cyclodextrin technique. The solubility of B-CD is 3 x higher solubility than the other formulation. Cyclodextr in molecule can generate a hydrophilic external surface and non-polar internal cavity. Therefore, when drug interacts with cyclodextrin molecule, drug will be entrapped inside cyclodexrin cavity to form a stable inclusion complex, thereby improving solubility of poorly water soluble drugs. Nanosuspension technique reduces drug particle size, thus increasing drug's water solubility (Shivhare*et al.,* 2009).

The in vitro permeability study was conducted by using Franz diffusion cell. 3 cells were used to conduct the test. Temperature of the diffusion medium (water) was maintained at 32^{o}C. Phosphate-buffered saline (pH7.4) was used as receptor fluid. The cellusose nitrate membrane was used as skin membrane. 1g of gel was applied onto the donor compartment. Samples are collected over 6 hours and analyzed by using UV spectrophotometer at 262nm. Sample was collected at 30min, 1hour, 2 hour , 4 hour, 5hour and 6 hour. The sample was collected using the 1mL syringe. The 1mL withdrawn was then replaced using the Phosphate Buffer Solution with the ph of 7.64. From the sample collected 0.2mL was transfer into a test tube and diluted with 2mL of Phosphate Buffer Solution. The remaining 0.8mL was then transfer into another test tube. An average of 3 readings was taken using the UV-VIS at the wavelength of 264nm for the concentrated and the diluted. The sample collected was then covered carefully with the aluminum foil to avoid any photosensitivity that could affect the reading. The results showed that maximum of 23.13 % of drug was released from the nanosuspension technique. This test was conducted over 6 hours and the sample were collected at 30min, 1 hour, 2-hour, 4-hour, 5 hour and 6 hours. The maximum amount of drug release on B-Cyclodextrin is 9.38% on the 6th hour. Although the solubility was higher in B-cyclodextrin but the drug release was higher in nanosuspension. This is because our skin is lipophilic in nature, there a B-Cyclodextrin with a higher solubility in water makes it difficult to pass through the membrane to reach the site of action (Helal*et al.,* 2012). The pH of the gel was measured using the ph meter. All the gels has a ph range of 7. pH 7 is acceptable to the body and safe to use. Throughout the period of study, the gel remained stable without any discoloration or precipitation.

CONCLUSION

Indomethacin active ingredient can be formulated into stable gel .Nanosuspension technique significantly improves solubility, and permeability of Indomethacin. Cyclodextrin inclusion

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technique only greatly increase solubility of Indomethacin but showed no significance difference in permeability. In terms of solubility, effect of cyclodextrin inclusion complex is better compared to nanosuspension. In a nutshell, nanosuspension is the right choice of technique to enhance the drug's drug bioavailability and solubility to relieve pain within few hours of application to the skin. On the basis of the present finding, both techniques applied possess the capabilities to increase the solubility of the poorly soluble drugs. Regardless, this research will serve as a reference point in the literature for time to come.

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