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A RESEARCH ARTICLE ON FORMULATION AND EVALUATION OF INDOMETHACIN SOLID DISPERSIONS

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ABSTRACT

The Biopharmaceutical Classification System (BCS) divides drugs into one of four classes according to their solubility and permeability. Solid dispersion can be defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melt, solvent or solvent-melt method. In the current research Indomethacin solid dispersions are prepared and evaluated for better solubility and bioavailability.

KEYWORDS

BCS Classification, Solid dispersion, Indomethacin, Solubility and Bioavailability.

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INTRODUCTION

The term solid dispersion can be defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melt, solvent or solvent-melt method. The definition has now been extended to include certain nanoparticles, microspheres, microcapsules and other dispersions of drugs in polymers.

Advantages of solid dispersions

Rapid dissolution rate that result in an increase in the rate and extent of the absorption of the drug and a reduction in pre-systemic metabolism. This latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug as in the

case of 17-β-estradiol or inhibition of the enzyme by the carrier as in the case of morphine-tristear in dispersion. Both can lead to lower doses of the drug.

Transformation of the liquid form of the drug into a solid from. For eg: Clofibrate and benzyl benzoate can be incorporated into PEG 6000 to give a Solid.

Avoidance of polymorphic changes and there by bioavailability problems as in the case of Nabilone and PVP dispersion. Protection of certain drugs by PEGs. Eg: cardiac glycosides against decomposition by saliva to allow buccal absorption.

Classification of Solid Dispersions

Solid dispersions can be classified as follows:

- Simple eutectic mixture
- Solid solution
- Glass solution or suspension
- Compound or complex formation
- Amorphous precipitation
- Combination of any of the above

Solid solutions can be further divided based on whether the formulation is a continuous or a discontinuous solid solution. Further they can be divided based on whether the formulation is a substitutional crystalline, interstitial crystalline or amorphous solid solution.

MATERIALS AND METHODS

The required materials and equipment's are listed in the Table No.1,2.

Methodology

Preformulation study

Preformulation study is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies (IR Studies) were performed.

Method for Preparation of Solid Dispersions

Two different methods were used to prepare the three solid dispersions, two for Indomethacin. Four different concentrations were prepared for each of the three solid dispersions to determine the effect of change of concentrations of the drug and the carrier on the release rate of the drug from the dose. Neusilin® US2 was used as an adsorbent to make the solid dispersions ready for any further pharmaceutical preparation, without any processing.

Method for Preparing the Solid Dispersions with Indomethacin and Urea

Four formulations utilizing various ratios of Indomethacin and urea were made. The ratios for Indomethacin and urea used to make the solid dispersions were 1:9, 3:7, 1:1 and 7:3 for Indomethacin and urea, respectively. An amount of Neusilin®US2 was double the weight of Indomethacin used in that formulation. These solid dispersions were made by the solvent evaporation method. In this method urea (the carrier) was heated to a temperature of1350 C and melted. Once the carrier was molten, the drug, Indomethacin was added to the molten carrier and mixed thoroughly until a clear solution was formed. Once a clear solution was formed, Neusilin®US2 which was pre-heated to 135^0C was added to the solid dispersion. The mix was then thoroughly mixed to obtain an even dispersion of the solid dispersion on the adsorbent and then quench cooled by placing the mixture into a freezing mixture made with ice and salt. The finished product was then stored in an airtight container in a dark and cool place for further testing.

Method for Preparing the Solid Dispersions with Indomethacin and Kollidon®VA64

This formulation was made using the solvent evaporation method. The four different ratios of Indomethacin (drug) to Kollidone®VA64 (carrier) were 1:9; 3:7; 1:1 and 7:3. Indomethacin and Kollidone®VA64 were added to a beaker containing the required amount of ethanol (solvent). Once these two components were dissolved in the solvent, Neusilin®US2 (adsorbent) was added and thoroughly mixed. The amount of Neusilin®US2 was double the amount in weight of Indomethacin used. In the case of the first combination which is 1:9 Indomethacin: KollidonVA64®, the amount of Neusilin®US2 was four times the weight of Indomethacin. This was done to ensure that there was enough Neusilin®US2 for the amount of solution present. The slurry formed with the solution of Indomethacin and Kollidon®VA64 in ethanol, and Neusilin®US2 was then subjected to solvent removal by heat. The finished product is left in

a desiccator for a period of 24 hours in order for the complete removal of the solvent used. The product is then stored in an air tight container in a dark cool for further analysis.

EVALUATION

The formulations were evaluated for solubility studies, drug content and dissolution profile.

Dissolution Testing

All the dissolution tests were performed in triplicate. Dissolution studies for the solid dispersion granules were carried out using USP Type II apparatus dissolution apparatus at 37 ± 0.5ºC with a paddle rotation speed adjusted to 100 rpm.. Phosphate buffer at pH 7.6 made by dissolving 4.8 grams of Monobasic sodium phosphate and 14.7 grams of dibasic sodium phosphate in 1 L of water, was used to study the dissolution of Indomethacin. The sample size was chosen so as to keep the amount of drug constant at 50 mg for Indomethacin. Samples were drawn from the dissolution media at regular intervals and replaced with equal amounts of the buffer to maintain sink conditions. The withdrawn samples were passed through a 0.2 micron filter to get rid of any undissolved particles. This solution was then tested using UV-Visible spectroscopy to determine the dissolved amount of drug in the dissolution media.

RESULTS AND DISCUSSION

Melting point determination

Melting point of Indomethacin was determined by using digital melting point apparatus by capillary method. The melting point of famotidine was found to be 155-162^{0}C. Thus obtained melting point is in agreement with literature melting point containing the purity of drug.

Drug excipient compatibility study

This performulation study was carried out to study the compatibility of the pure drug Indomethacin with polymer prior to the formulation. All these peaks were also found into the drug polymer mixture. FTIR has been used to assess the interaction between carrier and guest molecules in the solid state showed in figure No.1, 2.

Solubility study

The solubility data of pure Indomethacin, solid dispersion by solvent evaporation method are given in the Table No.3. The solubility data shows that concentration of polymer increases solubility increases.

Drug content

The results of drug content are given in the Table No.4. The drug content was ranged from 93.47 to 99.63.The drug all the prepared solid dispersions were found to be fine and free flowing, with low standard deviation values in% drug content ensured uniformity of drug content in each batch, all the dispersions contained 95.5% of the drug.

Dissolution study

Invitro dissolution of Indomethacin from solid dispersions containing various ratios of drug to urea, Kollidion. The *invitro* dissolution study of the solid dispersions was carried in p^H 7.6 from 0-60 mins by USP type II apparatus and the values were shown in table. The plot of % cum amount of drug releases vs. time shown in the figure and Table No.5 and 6. As the concentration of urea increases cumulative % also increases. As the concentration of Kollidion increases cumulative % also decreases.

Table No.1: List of Materials

S.No	Materials	Manufacture
1	Indomethacin	Nobel pharmaceutical, India
2	Urea	RFCL. Limited, New Delhi
3	Kollidion	BASF Germany.
4	Ethanol	Finar chemicals, Limited

All the chemicals used in this study were analytical grade

Table No.2: List of Equipments

S.No	EQUIPMENT	MANUFACTURE
1	Melting point apparatus	DBK Instruments Mumbai
2	Digital balance	Shimadzu instruments, Mumbai.
3	Dissolution apparatus	Electro Lab.(USP XX III) (DTD– 06P),Mumbai.
4	Hot air oven	M. C. Dallal, Chennai
5	Uv -spectrophotometer	UV-1800 Shimadzu spectrophotometer. Japan

Table No.3: Solubility Study of Indomethacin Solid Dispersions

S.No	Formulation code	Solubility
1	Pure drug	189.0
2	F1	210.78
3	F2	215.82
4	F3	270.09
5	F4	275.21
6	F5	319.01
7	F6	274.91
8	F7	291.67
9	F8	320.17

Table No.4: Drug Content Study of Indomethacin Solid Dispersions

S.No	Formulation code	Drug content (%)
1	F1	96.29±1.75
2	F2	94.71±1.32
3	F3	93.47±0.96
4	F4	99.89±2.73
5	F5	92.29±3.02
6	F6	94.46±2.89
7	F7	95.93±3.82
8	F8	97.36±2.94

Table No.5: *Invitro* Dissolution Profile of Indomethacin + Urea Solid Dispersions

S.No	TIME	DRUG	F1	F2	F3	F4
1	0	0	0	0	0	0
2	5	12.6	62.4	60.8	45.3	41.5
3	10	31.9	76.2	75.3	66.6	57.0
4	15	40.6	85.2	84.1	72.7	65.9
5	30	55.8	89.7	85.8	77.9	73.7
6	45	66.2	93.4	91.9	85.0	79.0
7	60	75.1	95.2	94.9	87.5	85.0
8	90	81.4	97.2	96.7	92.9	90.1
9	120	82.1	98.6	97.7	93.4	91.4

Table No.6: *Invitro* Dissolution Profile of Indomethacin + Kollidon Solid Dispersions

S.No	Time	Drug	F5	F6	F7	F8
1	0	0	0	0	0	0
2	5	12.6	62.3	60.8	47.2	43.5
3	10	31.9	72.2	71.5	67.9	58.2
4	15	40.6	83.9	82.2	73.6	70.8
5	30	55.8	88.6	84.2	79.8	76.6
6	45	66.2	92.8	90.0	85.7	81.1
7	60	75.1	94.2	94.3	88.4	86.6
8	90	81.4	95.9	95.8	93.8	91.0
9	120	82.1	97.0	96.6	94.4	91.4

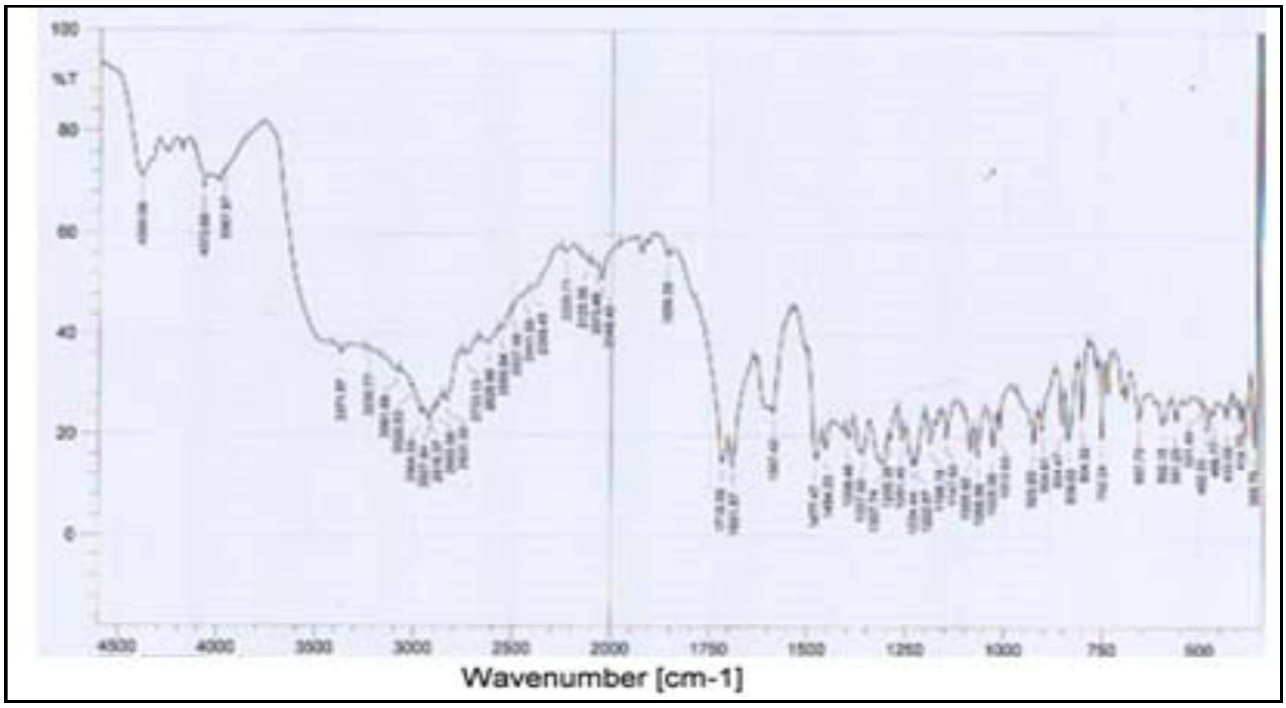

Figure No.1: FTIR Spectra of Mixture of Best Formulation with Urea

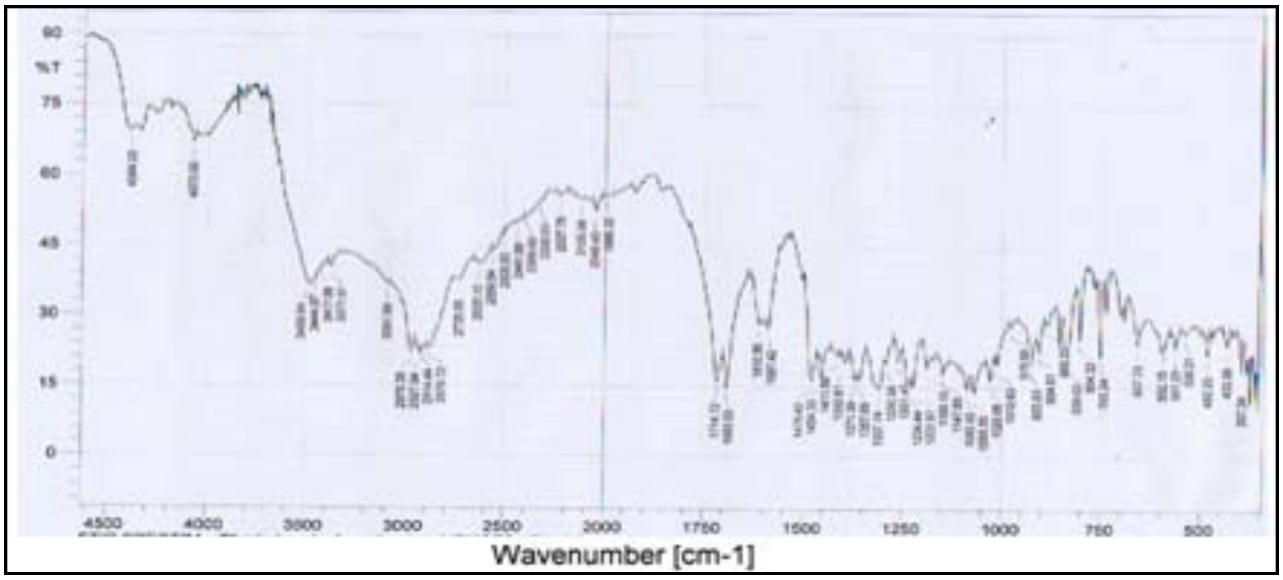

Figure No.2: FTIR Spectra of Mixture of Best Formulation with Kollidon

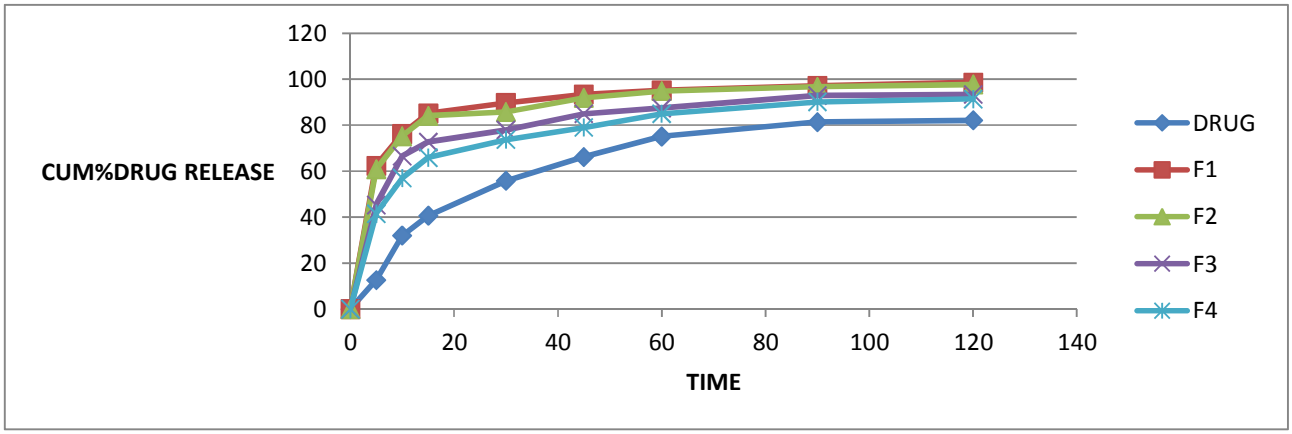

Figure No.3: *Invitro* Dissolution Profile of Formulations F1 - F4.

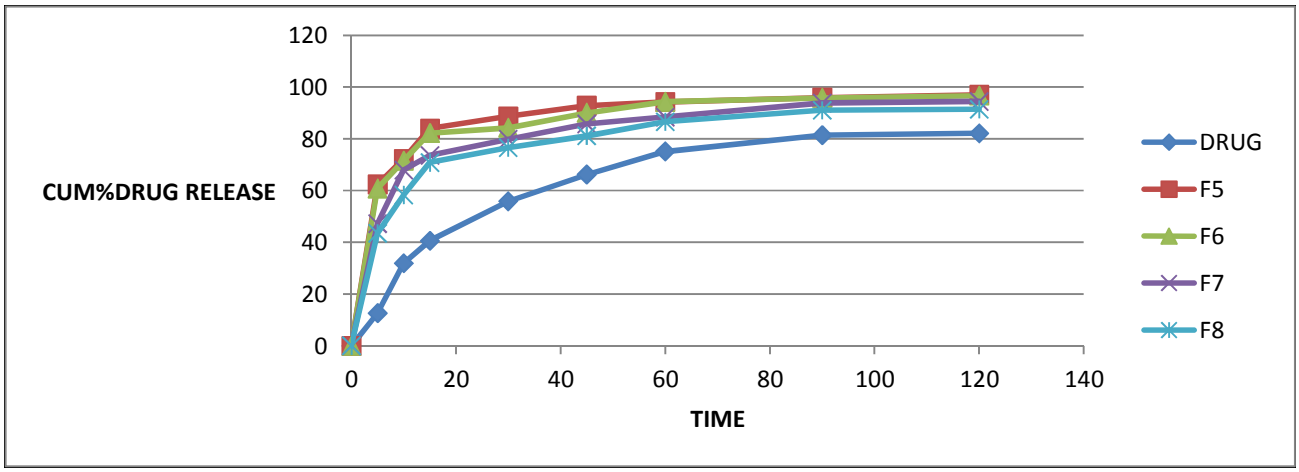

Figure No.4: *Invitro* Dissolution Profile of Formulations F5 - F8

CONCLUSION

The ultimate aim of this research work by using the polymers like urea and Kollidion can be used as a potential carrier in the dissolution rate enhancement using model drug as a Indomethacin. Hence prepared the solid dispersion by physical mixture, solvent evaporation methods using carriers like urea, Kollidion. In Preformulation studies it was found that Indomethacin is having more solubility in pH 7.6 for the estimation of drug content, solubility study and *in vitro* release studies. FTIR studies confirm that there was no interaction between drug and carriers used in the preparation of Indomethacin solid dispersion.

The concentration of various carriers have direct effect on dissolution rate that it as the concentration of carriers increased, the solubility, drug content also increased.

In vitro dissolution studies of the prepared formulation of Indomethacin improve the dissolution characteristics in urea than Kollidion.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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