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RESEARCH ARTICLE

Solubility Enhancement of Diflunisal by Solid Dispersion Techniques

Krishnamurthy Kamalapurkar[1], Pooja Vijaykumar Padwal[1], Neha Amarsingh Chauhan[1], Madhuri Pandurang Alte[1], Akshay Sudhakar Dhupad[1]

[1]*Department of Pharmaceutics, D.S.T.S. Mandal's College of Pharmacy, Solapur, Maharashtra, India.*

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ABSTRACT

The study was carried out with a view to enhance dissolution rate of poorly water soluble drug by preparing tablets of solid dispersion of Diflunisal. The solid dispersion was prepared by using carriers like Crosspovidone, PEG and Urea. The solid dispersion was prepared by Physical mixture, Fusion, Kneading and Solvent evaporation methods using different ratio of Diflunisal and carrier. The optimized solid dispersion batch F8 and F9 were incorporated into tablets for faster release of Diflunisal. *In-vitro* dissolution rate of both batches of Diflunisal from solid dispersion was found to be 99.49 % and 98.90 % drug release after 2 hr compared to 46.27% release shown by pure drug after 2 hr.

KEYWORDS

Diflunisal, Urea, Physical mixture, Solvent evaporation method

INTRODUCTION

Drugs that undergo dissolution rate limited Gastrointestinal absorption generally show improved dissolution and bioavailability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in pure wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have reduced the incidence of these problems and enhanced dissolution[1.] The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Solid dispersion has great potential for both increasing the bioavailability of drug and developing controlled release preparations. Thus to solve bioavailability issues with respect to poorly water soluble drugs solid dispersion technology has grown rapidly. The dosage form can be developed and prepared using small amounts of drugs substances in early stages of the drug development process the system might have an advantage over such other commonly used bioavailability enhancement technique as micronization of drugs and soft gelatin encapsulation. Aim of the present work is to enhance the solubility of Diflunisal by Solid dispersion techniques and to formulate a dosage form containing Diflunisal which is stable and has improved dissolution rate.

*Address for Correspondence:
Pooja Vijaykumar Padwal
Department of Pharmaceutics, D.S.T.S. Mandal's College of Pharmacy, Solapur, Maharashtra, India.
E mail ID: poojapadwal490@gmail.com

Advantages

a. Reduced particle size.

b. Improved wettability.

c. Improved porosity of drug.

Conversion crystalline structure of drug in to amorphous form.[3]

MATERIAL & METHODS

Materials

Diflunisal were obtained from Arti Industries Ltd, Thane, India. Tris (hydroxymethyl) amino meth, Urea, Lactose was obtained from Ozone International Mumbai, India. Citric acid was obtained from Vijay Chemical Industry, Solapur, Maharashtra, India. Crosspovidone, PEG, Methanol, Polyvinyl pyrrolidone, Mannitol were obtained from Research lab fine chemical Industry, Mumbai, Maharashtra, India. Talc, Magnesium stearate were obtained from Vikash Pharma, Mumbai, Maharashtra, India.

Methods

Different formulations of solid dispersions of Diflunisal were prepared with four different polymers as carrier by four methods, viz. Physical mixture, Melt fusion (MF) method and Solvent evaporation (SE). The compositions of the formulations are shown in Table 1.

Physical Mixture

Physical mixture was prepared by mixing the Diflunisal : Crosspovidone in 1:1, 1:2, 1:3 ratios in mortar and pestle and passed through sieve #60 and the tablets were formulated using direct compression method.

Fusion Method

Accurately weighed amount of carrier was placed on a hot plate and molten, with constant stirring, maintaining the critical temperature just below 70°C. An accurately weighed amount of Diflunisal was incorporated into the molten carrier with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. It was cooled in an ice-bath, allowed to solidify and sieved through sieve 60# and the tablets were formulated using direct compression method.

Solvent Evaporation Method

The Diflunisal : Urea in 1:1, 1:2, 1:3 ratio was dissolved in sufficient volume of methanol with continuous stirring. The resulting mixture was transferred into petridish and evaporation of the solvents was carried out by keeping the petridish at room temperature. The mass obtained was crushed and passed through sieve 44# and the tablets were formulated using direct compression method.

Formulation of Solid Dispersion

Table 1: Formulation of Solid Dispersion

Method	Carrier	Batch	Ratio (Drug: Carrier) mg
Physical Mixture	Crosspovidone	**F1**	250:250
		F2	250:500
		F3	250:750
Fusion method	PEG	**F4**	250:250
		F5	250:500
		F6	250:750
Solvent evaporation method	Urea	**F7**	250:250
		F8	250:500
		F9	250:750

Characteristics of Solid Dispersion Complex[3]

Bulk Density (Db)

Accurate weighed amount of solid dispersion preparation of different ratios were poured in to 25 ml of measuring cylinder and bulk volume was noted and then calculated by the following equation

$$Db = Mass/Bulk\ volume$$

Tapped Density (Dt)

Accurate weighed amount of solid dispersion preparation of different ratios were poured in to

25 ml of measuring cylinder and then tapped for 750 times and the tapped volume was noted and calculated by the following equation.

Dt = Mass of powder/Tapped volume

Compressibility Index

$$I = [(Vb – Vt)/ Vb] \times 100$$

Where, I is the Compressibility index, Vb is the bulk volume of powder, Vt is the tapped volume of the powder.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner ratio = Dt/Db

Where, Dt is the tapped density, Db is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of Repose

Angle of repose was determined using fixed funnel method. The solid dispersion was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of heap (r) was measured and angle of repose was calculated by using the following equation.

$$\theta = Tan^{-1} h/r$$

Table 2: Characteristics of Solid dispersion complex

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Haushner Ratio (%)	Angle of Repose (θ)
F1	0.3154±0.0050	0.3751±0.0103	15±0.0108	1.1889±0.0214	27.77±0.2598
F2	0.3100±0.0062	0.3693±0.0090	14±0.0152	1.1800±0.0176	29.10±0.5022
F3	0.3077±0.0039	0.3077±0.0039	15±0.0100	1.1912±0.0292	29.38±0.2540
F4	0.3051±0.0103	0.3554±0.0050	13±0.0108	1.1689±0.0214	27.57±0.2598
F5	0.3193±0.0090	0.3400±0.0062	14±0.0152	1.1080±0.0176	29.20±0.5022
F6	0.3265±0.0056	0.3577±0.0039	12±0.0100	1.1712±0.0292	29.48±0.2540
F7	0.3091±0.0103	0.3554±0.0050	13±0.0108	1.1689±0.0214	27.57±0.2598
F8	0.3139±0.0090	0.3300±0.0062	14±0.0152	1.1580±0.0176	26.20±0.5022
F9	0.3065±0.0056	0.3677±0.0039	12±0.0100	1.1712±0.0292	29.48±0.2540

Formulation of Optimized Batch

Table 3: Formulation Of the Optimize Batch F8 and F9 of Tablet

Sr.no.	Ingredients	Quantity given in (mg)	
		F8	F9
1.	Solid Dispersion Complex	750	800
2.	PVP	10	10
3.	Lactose	10	10
4.	Talc	10	10
5.	Magnesium stearate	10	10
6.	Mannitol	5	5
7.	Sodium starch glycolate	5	5

RESULTS AND DISCUSSION

Calibration curve of Diflunisal

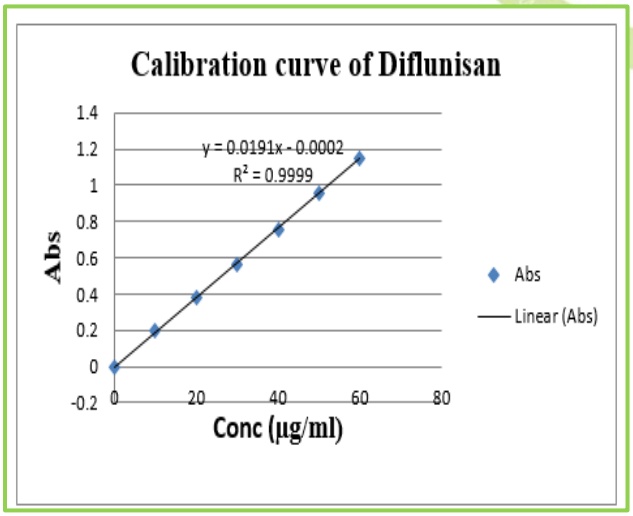

Figure 1: Standard curve of Diflunisal

Calibration curve of Diflunisal was found to be linear in concentrations between 10 to 60 µg/ml with equation y = 0.019 and coefficient R^2 = 0.999.

In-vitro Dissolution Study of Solid Dispersion

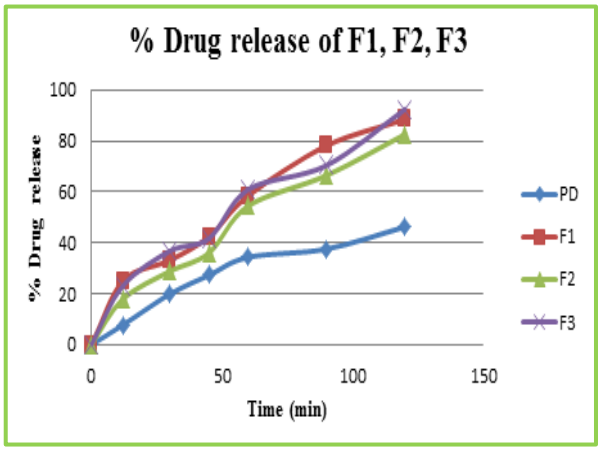

Figure 2: Dissolution profile of Solid dispersion pure drug F1, F2, F3

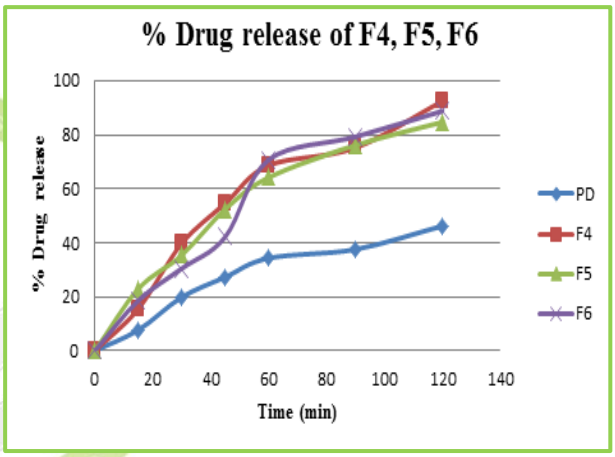

Figure 3: Dissolution profile of Solid dispersion pure drug F4, F5, F6

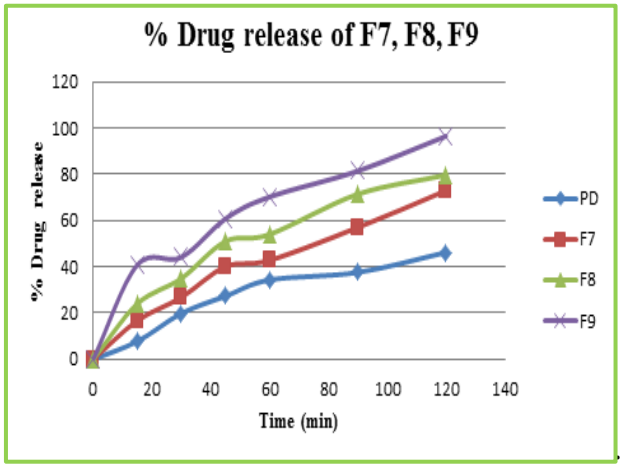

Figure 4: Dissolution profile of Solid dispersion pure drug F7, F8, F9

Table 4: *In-vitro* Dissolution study of Solid dispersion batches F1 to F6

Time (min)	Pure drug	F1	F2	F3	F4	F5	F6
12	7.7	25.04	17.84	23.06	15.54	22.95	18.57
30	19.87	33.17	28.80	36.76	39.75	35.40	30.47
45	27.29	42.46	36.06	41.77	54.58	52.41	42.12
60	34.33	58.48	54.53	61.00	68.67	64.18	70.76
90	37.60	78.19	66.52	70.42	75.21	76.13	79.29
120	46.27	88.48	82.65	92.53	92.53	84.69	88.81

Table 5: *In-vitro* dissolution study of Solid dispersion batches F7 to F9

Time (min)	Pure drug	F7	F8	F9
15	7.7	16.69	24.00	40.81
30	19.87	26.81	34.99	44.18
45	27.29	40.11	51.05	60.83
60	34.33	42.84	54.05	70.32
90	37.60	57.06	71.48	81.52
120	46.27	73.04	79.80	96.61

Evaluation of Solid Dispersion Tablet

Table 6: Post compression parameters of prepared Tablet

Batch	Weight Variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	(%) Drug Content
F1	802±0.25	12.00±0.11	7.0±0.10	0.12±0.3	98.00
F2	798±0.20	13.00±0.25	7.0±0.12	0.28±0.2	97.32
F3	799±0.60	12.50±0.50	7.5±0.25	0.29±0.6	96.22
F4	803±0.45	11.80±0.01	7.0±0.29	0.36±0.8	99.01
F5	801±0.12	12.00±0.05	6.5±0.28	0.35±0.4	98.67
F6	800±0.19	12.25±0.15	7.0±0.35	0.62±0.4	97.45
F7	803±0.25	13.25±0.28	7.5±0.50	0.29±0.1	97.89
F8	795±0.12	12.50±0.30	7.0±0.20	0.11±0.2	99.49
F9	803±0.85	12.00±0.27	7.0±000	0.12±0.5	98.90

Uniformity of Weight

Uniformity of weight revealed that the tablets of all formulations were within the range of Pharmacopoeial specification. F8 and F9 formulations pass uniformity of weight.

Tablet Hardness

The tablet hardness are shown in table 6.

Tablet Thickness

The thickness was found to be in between 11 mm to 12 mm for both formulations. The thickness of the tablet depends upon the diameter of die, the amount of fill permitted to enter the die, the compaction characteristic of the fill material and the force applied during compression.

Drug Content Uniformity

The drug content uniformity was performed for F8 and F9 prepared solid dispersion tablet by direct compression method. The % drug content were found 99.49% and 98.90% of Diflunisal. The % drug content data estimated for the prepared tablets were in the prescribed limits.

Tablet Friability

Friability is related to tablet ability to withstand both shock and abrasion without physical damage during the handling of manufacturing, packaging, shipment and consumer use. Friability of formulations shows 0.112 and 0.125 respectively for F8 and F12 batch. All value of friability lie between the prescribed limits (0.1-0.9%).

***In-vitro* Dissolution Study**

Dissolution study of tablets was performed in USP type-II (paddle) dissolution test apparatus using 900 ml of 0.1M Tris buffer pH 7.2 as dissolution media. The tablets were loaded into each basket of dissolution apparatus; the temperature of dissolution media was maintained at 37.5±0.5˚C with stirring speed of 50 rpm throughout the study. The 5ml samples were withdrawn at a suitable interval of time and analysed by UV- Visible spectrophotometer at 228 nm.

Dissolution Parameter

Medium: ph 7.2 0.1M tris buffer.

Apparatus: USP type II (paddle).

Speed: 50 rpm.

Time points: 15, 30, 45, 60, 90, 120 min.

Temperature: 37± 0.5˚C

Stability Study

Stability studies revealed that there was no significant change found in color, hardness, drug content and in-vitro drug release of Diflunisan tablets even after stored at 25±2˚C/60±5% RH and 40±2˚C/75±5% RH for 45 days. The results proved that there was no significant effect of storage temperature on the drug release.

CONCLUSION

The objective of presence study was to improve the solubility and dissolution rate of poorly soluble drug Diflunisal by using Crosspovidone, PEG, and Urea as carriers. The formulation of F8 and F9 batch shows good % drug release (99.49 and 98.90% respectively) from solid dispersion techniques after 2 hr compared to 46.27% release shown by pure drug after 2 hr.. The tablets were prepared by using sodium starch glycolate as super disintegrant by direct compression method. The optimized F8 and F9 batch shows excellent solubility, dissolution rate and drug content than the other batches. Thus it can be concluded the solubility of the poorly soluble drug Diflunisal can be improved by using solid dispersion technique and the carrier urea has increased the dissolution rate of the drug without any drug interaction.

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