Original Article

Formulation And Optimization Dispersible Tablets Using Of Solid Dispersions Of Poorly Water-Soluble Drug Etoricoxib

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Abstract

The aim of this research study was to formulate and optimize solid dispersions to improve the solubility of poorly soluble drugs. Solid dispersion, a technique involving the dispersion of such drugs in a solid matrix, was employed using various water-soluble carriers, including poloxamer 188, poloxamer 407, PEG 4000, and PEG 6000, in different ratios. The prepared solid dispersions were evaluated for physical appearance, drug lodging, solubility, and drug release. Among the different formulations, the F11 formulation demonstrated optimized results. Subsequently, the F11 formulation of the solid dispersion was utilized in the preparation of dispersible tablets. Super disintegrating agents, namely Crospovidone and SSG (sodium starch glycolate), were incorporated in different ratios (10, 15, and 20). The dispersible tablets were formulated using the direct compression method. Comprehensive precompression and post-compression evaluations were performed to ensure the quality and optimization of the tablets. Upon completion of the evaluation process, it was observed that the F2 formulation displayed the most favorable outcomes among the dispersible tablet formulations. Consequently, the conclusion was drawn that the F2 formulation of the dispersible tablet, containing the optimized solid dispersion, exhibited improved solubility, drug release, and overall performance. These findings highlight the potential of solid dispersions and dispersible tablets as effective strategies for enhancing the bioavailability and formulation properties of poorly soluble drugs.

Keyword: Poorly soluble, solid dispersion, dispersible tablet, solubility enhancement etc.

INTRODUCTION [1-2]:

Dispersible tablets are uncoated or film coated tablets intended to be dispersed in water prior to administration, giving a homogenous dispersion. Dispersion tablets are also called soluble tablets 'Solvella'. They may contain permitted colouring matter and flavorings agents.

"Dispersible tablets are uncoated or film-coated tablets that can be dispersed in liquid before administration giving a homogenous dispersion." Dispersible tablets usually disintegrate within three minutes when put in water or a small amount of breast milk.

"Dispersible tablet is a pharmaceutical dosage form that is designed to rapid disintegrate in a liquid, typically water, to form a homogeneous suspension or solution. These tablets are formulated to be easily and conveniently administered by dispersing them in a liquid before ingestion.

ADVANTAGES OF DISPERSIBLE TABLET: -

1. Fast onset action compared with conventional tablets and improved bioavailability of tablet.
2. Suitable for children and elderly persons with swallowing difficulties Dispersible tablets can be administered to children conveniently without any swallowing difficulty and is an important factor, as Dispersible Tablets can achieve an exact and required dose.
3. Dispersible tablets remain solid until administration. This aids the stability of the pharmaceutically active agent, the dose accuracy, and storage of the tablets.
4. Dispersible tablet are formulated with an objective of improving the dissolution of poorly soluble drugs by using various disintegrate.
5. Manufacturing cost is low in compression to other dosage form.

DISADVANTAGE: Dispersible tablets have less physical resistance than regular tablets; they are more sensitive to moisture and may degrade at higher humidity conditions. Each tablet must be protected from the ambient humidity.

FORMULATION OF DISPERSIBLE TABLET [3-5]: Dispersible tablets are formulated using a combination of active pharmaceutical ingredients (APIs) and various excipients. The excipients play essential roles in the formulation, aiding in tablet disintegration, dissolution, taste masking, stability, and overall tablet performance. Here are the common components of dispersible tablets:

1. ACTIVE PHARMACEUTICAL INGREDIENT (API) [6]: The API is the therapeutic substance that provides the desired pharmacological effect. It is the primary active component in the dispersible tablet.
2. DILUENTS/FILLERS [7]: Diluents or fillers are added to the formulation to increase the bulk volume of the tablet. They facilitate the uniform distribution of the API and other excipients and provide the required tablet weight and hardness. Common diluents include lactose, mannitol, microcrystalline cellulose, and sorbitol.
3. SUPER DISINTEGRANTS [8]: Super disintegrants promote rapid tablet disintegration and dissolution when in contact with water. They help to break down the tablet into smaller particles or granules, forming a suspension or solution. Examples of super disintegrants include crospovidone, croscarmellose sodium, sodium starch glycolate, and cross-linked carboxymethylcellulose.
4. BINDERS [9]: Binders are used to hold the tablet ingredients together and provide cohesion during compression. They enhance tablet strength and prevent tablet fragmentation. Common binders include microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone.
5. DISINTEGRANTS [10]: Disintegrants help to break down the tablet into smaller particles when in contact with water. They facilitate the rapid dispersion of the tablet in a liquid medium. Common disintegrants include croscarmellose sodium, sodium starch glycolate, crospovidone, and low-substituted hydroxypropyl cellulose.
6. LUBRICANTS: Lubricants reduce friction between the tablet formulation and the tablet press machine during compression. They prevent sticking or adhesion, allowing for smooth tablet ejection. Examples of lubricants include magnesium stearate, stearic acid, talc, and sodium stearyl fumarate.
7. FLAVORS AND SWEETENERS: Flavors and sweeteners may be added to improve the taste of the tablet, making it more palatable for patients. Commonly used flavors include mint, fruit, or vanilla, and sweeteners such as aspartame or sucralose.
8. COLORING AGENTS: Coloring agents are added to provide visual identification and aesthetic appeal to the dispersible tablet. They are optional and can include various FDA-approved colorants.

MATERIAL AND METHOD: drug etoricoxib gift sample of obtained from Alkem Pharmaceuticals, Mumbai , PEG 6000,PEG 4000 Nice chemicals, Kochi and Poloxamer-188 , Polomer 407 obtained SD fine chemical Hyderabad , Crospovidone and SSG and other chemical from PG lab Indore .

SOLID DISPERSION [11-13]: Solid dispersion is a pharmaceutical technique used to enhance the solubility and bioavailability of poorly water-soluble drugs. It involves dispersing the drug in a solid matrix or carrier material to improve its dissolution and absorption characteristics. In a solid dispersion, the drug is molecularly dispersed or distributed within a hydrophilic carrier material, which could be a polymer or a mixture of polymers. The carrier material acts as a solubilizing agent, facilitating the dissolution of the drug in the gastrointestinal fluid upon oral administration.

THE DISPERSION CAN BE PREPARED USING VARIOUS METHODS [3-5]

1. MELTING METHOD: The drug and carrier material are melted together, mixed thoroughly, and then cooled to form a solid mass. This method is suitable for drugs and carriers with compatible melting points.

2. SOLVENT EVAPORATION METHOD: The drug and carrier material are dissolved in a common solvent, which is then evaporated to obtain a solid dispersion. This method is useful when the drug and carrier are not compatible at high temperatures.

ADVANTAGES OF SOLID DISPERSION INCLUDE:

1. Enhanced solubility: Solid dispersion increases the surface area of the drug, leading to improved dissolution rates and increased solubility.
2. Increased bioavailability: The enhanced dissolution of the drug improves its absorption in the gastrointestinal tract, leading to higher bioavailability and therapeutic effectiveness.
3. Formulation flexibility: Solid dispersion allows for the incorporation of a wide range of drug molecules, including poorly water-soluble drugs, into a solid dosage form.

DIS -ADVANTAGES OF SOLID DISPERSION INCLUDE:

1. Limited Compatibility: Solid dispersions can face challenges related to compatibility between the drug and the carrier or matrix used in the formulation. Some drugs may not readily dissolve or disperse in the chosen carrier, leading to poor drug release or reduced bioavailability.
2. Stability Concerns: Solid dispersions can be prone to stability issues, such as drug degradation, recrystallization, or phase separation. These concerns can impact the shelf life and efficacy of the medication, especially when exposed to conditions like temperature, humidity, or light.

Table :1 formulation Solid dispersions drug Etoricoxib .

Batch CodeSD	Composition	Method	Ratio
F1	Etoricoxib + Poloxamer-188	Fusion method of solid dispersion	1:1
F2	Etoricoxib + Poloxamer-188	Fusion method of solid dispersion	1:2
F3	Etoricoxib + Poloxamer-188	Fusion method of solid dispersion	1:4
F4	Etoricoxib + Poloxamer-188	Fusion method of solid dispersion	1:6
F5	Etoricoxib + Poloxamer-407	Fusion method of solid dispersion	1:1
F6	Etoricoxib + Poloxamer-407	Fusion method of solid dispersion	1:2
F7	Etoricoxib + Poloxamer-407	Fusion method of solid dispersion	1:4
F8	Etoricoxib + Poloxamer-407	Fusion method of solid dispersion	1:6
F9	Etoricoxib + PEG 4000	Fusion method of solid dispersion	1:1
F10	Etoricoxib + PEG 4000	Fusion method of solid dispersion	1:2
F11	Etoricoxib + PEG 4000	Fusion method of solid dispersion	1:4

F12	Etoricoxib + PEG 4000	Fusion method of solid dispersion	1:6
F13	Etoricoxib + PEG 6000	Fusion method of solid dispersion	1:1
F14	Etoricoxib + PEG 6000	Fusion method of solid dispersion	1:2
F15	Etoricoxib + PEG 6000	Fusion method of solid dispersion	1:4
F16	Etoricoxib + PEG 6000	Fusion method of solid dispersion	1:6

EVALUATION OF SOLID DISPERSION [13-14]:

MELTING POINT DETERMINATION BY CAPILLARY METHOD :

The capillary method is a common technique to determine the melting point of a substance. It involves filling a capillary tube with the substance, heating it gradually, and noting the temperature at which it changes from solid to liquid. This provides valuable information for substance identification and purity assessment.

Table :2 melting point of drug and water-soluble carrier

S no	Ingredient	Reported M.P^{0}C	Observed M.P^{0}C
1.	Etoricoxib	134-138	137
2.	Poloxamer-188	52-57	53
3.	Poloxamer-407	55-57	55
4.	PEG 6000	58-63	58
5.	PEG 4000	53-58	56

determine the wavelength of maximum (λmax) absorption. The λmax was found to be 233 nm against blank

STANDARD CALIBRATION CURVE :

Table 3 : Standard calibration data of Etoricoxib in 0.1N HCL solution 233 nm

S.NO	Concentration in □g/ml	Absorbance
1.	0	0
2.	2	0.125
3.	4	0.298
4.	6	0.471
6.	8	0.649
7.	10	0.889

Fourier Transform Infra-Red spectral analysis of drug sample : Drug excipient compatibility was analyzed using FT-IR. FT-IR was done using Perkin- Elmer spectrum. All the samples were mixed properly with KBr in 1:3 ratios and were made into pellets. Those pellets were analyzed. Each KBr disc was scanned over a wave number region of 4000-400 cm-1 using FT-IR Spectrophotometer.The FTIR spectra of Etoricoxib (alone) showed characteristic peaks at 1515.0 cm-1(C- N stretching vibration); 1445.5 cm-1, 1356.3 cm-1, 1156.6 cm-1 and 1082.3 cm-1 (S=0 stretching vibrations); and 845.4 cm-1, 776.8 cm-1 and 657.0 cm-1 (C-Cl stretching vibration), respectively

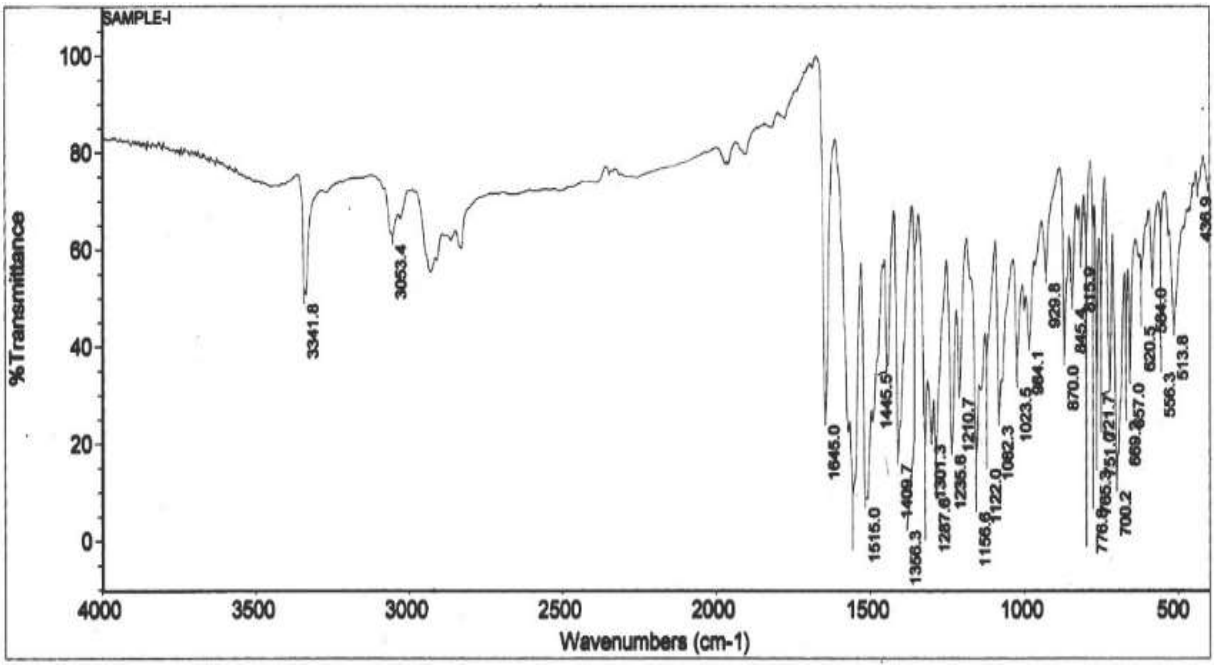

Fig.3 FTIR spectrum of etoricoxib reference

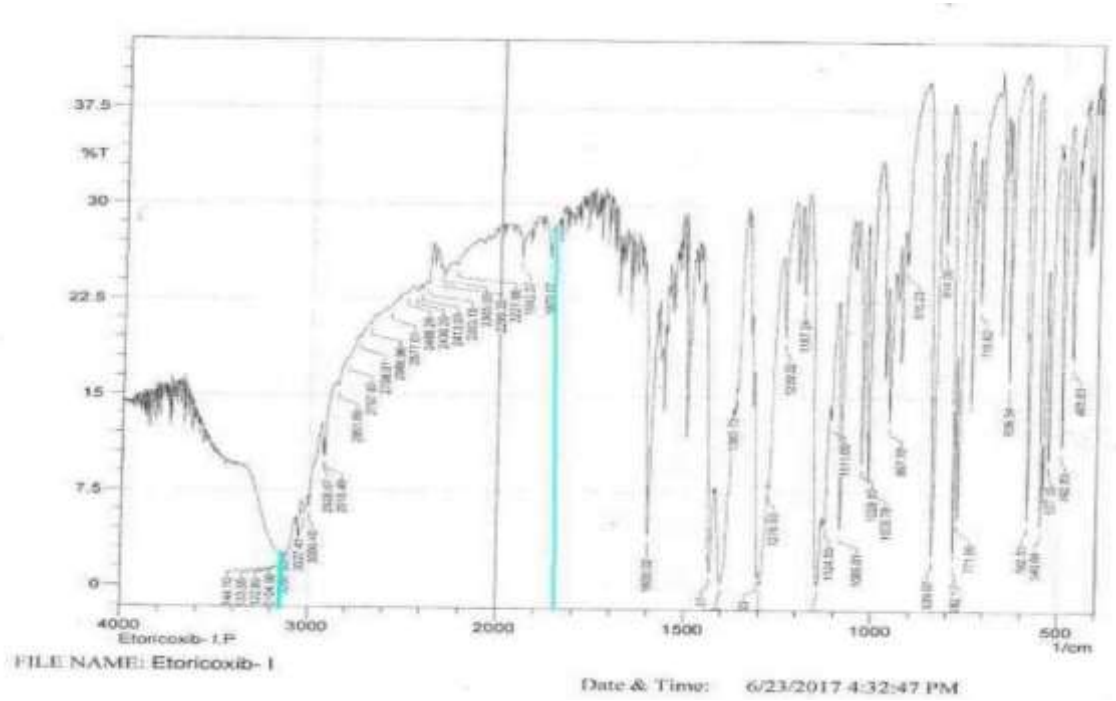

Fig.4 FTIR spectrum of etoricoxib sample drug.

DISSOLUTION PROFILE OF OPTIMIZED SOLID DISPERSION AMONG 16 FORMULATION [14-15]

Table 4 Dissolution profile of optimized solid dispersion

TIME MIN	**Cumulative% drug released**			
	ESDF9	ESDF10	ESDF11	ESDF12
0	0	0	0	0
5	18	20	33	34
10	28	30	43	45
15	38	43	54	55
20	39	58	64	65
25	41	61	73	74
30	52	72	83	84
35	62	82	91	91
40	72	91	97	97
45	82	98		
60	90			

Average three reding mean value recoded.

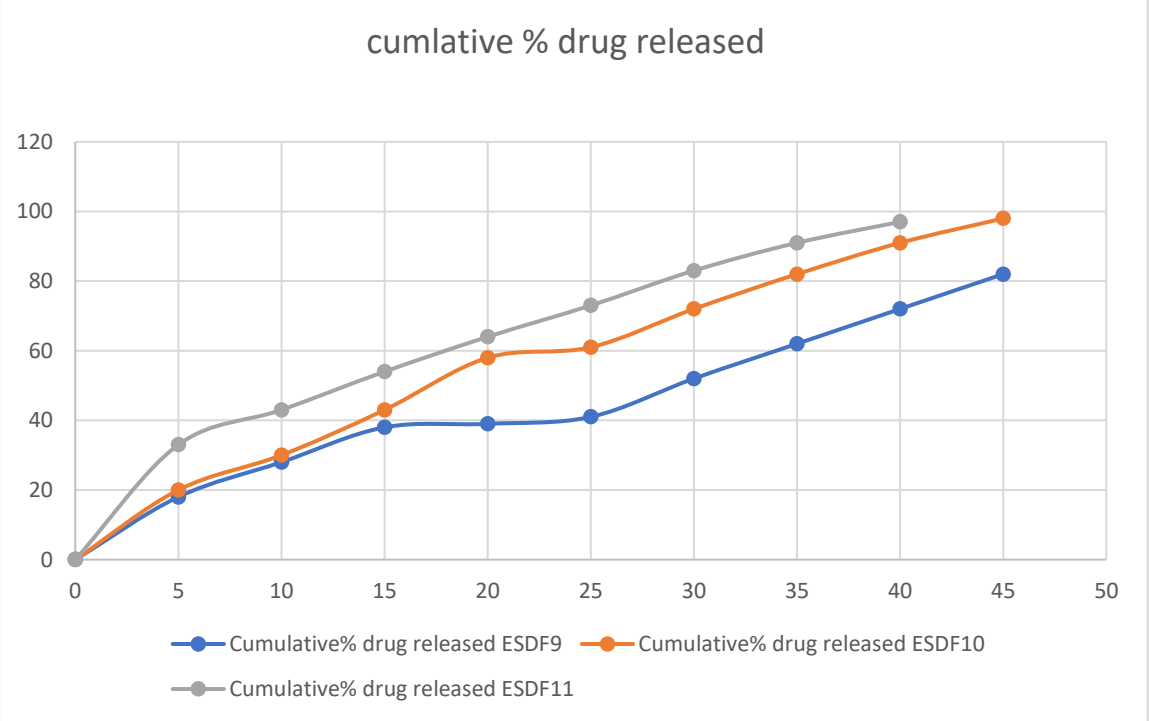

Fig 5 Dissolution profile of optimized solid dispersion

FORMULATION OF DISPERSIBLE TABLET [16-17]

DIRECT COMPRESSION METHOD:

The direct compression method is a common technique used for the preparation of dispersible tablets. It involves the direct compression of a blend of active pharmaceutical ingredient(s), excipients, and disintegrants into tablet form without the need for granulation or other pre-processing steps. Here's an overview of the direct compression method for dispersible tablet preparation:

1. Formulation: The formulation for a dispersible tablet includes the active pharmaceutical ingredient(s) (API), which provides the therapeutic effect, along with suitable excipients such

as binders, fillers, disintegrants, lubricants, and sweeteners. The choice of excipients depends on the characteristics of the API and the desired properties of the final tablet.

2. Selection of disintegrants: Disintegrants are essential in dispersible tablets as they facilitate the rapid breakup and dispersion of the tablet in a liquid medium. Commonly used disintegrants include croscarmellose sodium, crospovidone, sodium starch glycolate, and cross-linked PVP (polyvinylpyrrolidone).
3. Blend preparation: The API, excipients, and disintegrants are thoroughly mixed using suitable equipment such as a blender or a mixer. The blending process ensures homogeneity and uniform distribution of the components.
4. Lubrication: Lubricants such as magnesium stearate or stearic acid are often added to the blend to reduce friction between the particles during compression and to enhance the flow properties of the powder mixture. Lubricants should be added in small quantities to avoid adverse effects on tablet disintegration.
5. Compression: The blended powder mixture is compressed using a tablet press. The compression force and speed should be optimized to achieve tablets with suitable hardness and disintegration characteristics

MASTER FORMULA OF DISPERSIBLE TABLET

Table :5 Formula table of dispersible tablet by direct compression method

S NO	Ingredients in mg	F0	F1	F2	F3	F4	F5	F6
1.	Amount of solid dispersion equivalent to 30 mg drug (Drug: carrier) 1:4 Formulation SDF11	150	150	150	150	150	150	150
2.	Crosproidone	--	10	15	20	--	--	--
3.	Sodium starch glycolate (SSG)	--	--	--	--	10	15	20
4.	(Microcrystalline cellulose MCC)	35	35	35	35	35	35	35
5.	Lactose	Q.S	40	35	30	40	35	30
6.	Aerosil	3	3	3	3	3	3	3
7.	Talc	5	5	5	5	5	5	5
8.	Mg. stearate	5	5	5	5	5	5	5
9.	Aspartame	2	2	2	2	2	2	2
10.	flavoring agent	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	Total weight in mg	250	250	250	250	250	250	250

Evaluation of dispersible tablet Preformulating study of dispersible tablet [18-26]: Preformulating studies involve evaluating the physical, chemical, and biopharmaceutical properties of a drug candidate to determine its suitability for formulation development. These studies help identify potential issues and provide insights for optimizing the drug's formulation and delivery system, ensuring its safety, stability, and efficacy.

Table 6 Precompression evaluation of dispersible tablet:

Formulation code	Formulation code	Bulk density (g/cc)±SD	Tapped density(g/cc) ±SD	Carrs index ±SD	Hauser ratio ± SD
F0	0.568±0.89	0.853±0.78	34.65±0.43	17.94±0.74	1.28±0.67
F1	0.549±0.54	0.845±0.89	35.92±0.13	16.14±0.65	1.15±0.25
F2	0.579±0.32	0.850±0.56	36.46±0.31	17.94±0.73	1.26±0.19
F 3	0.579±0.29	0.842±0.76	35.09±0.78	16.14±0.62	1.25±0.04
F4	0.577±0.21	0.855±0.16	32.67±0.54	17.94±0.37	1.28±0.11
F5	0.575±0.67	0.851±0.65	37.53±0.70	17.94±0.36	1.11±0.87
F6	0.572±0.90	0.843±0.55	32.50±0.66	16.14±0.40	1.47±0.96

Table 7 Post compression evaluation of dispersible tablet :

Formulation Code	**Hardness (Kg/cm²) □ SD**	**Friability (%)**	**Thickness (mm) □SD**	**Weight variation (mg) □SD**
F0	5.0± 0.67	0.40	5.84±0.77	251±0.45
F1	4.1± 0.86	0.56	5.85±1.76	246±0.56
F2	4.1± 0.65	0.66	5.85±1.00	240±0.76
F3	4.2± 0.34	0.62	5.94±0.76	251±1.20
F4	4.0± 0.56	0.57	5.86±0.87	249±0.65
F5	4.1±0.73	0.47	5.86±0.99	248±0.67
F6	4.0± 1.10	0.67	5.85±0.34	250±0.98

Triplicate vale recoded

Table 8 Precompression evaluation of dispersible tablet

FormulationCode	**Drug Content (%) □SD**	**In vitro disintegrationtime (sec) □SD**	**Wetting time (sec) □ SD**
F0	99.63±0.99	212±1.50	185±0.87
F1	98.53±0.59	53±1.14	40±0.65
F2	98.33±0.78	52±0.34	35±0.45
F3	98.44±0.43	54±0.88	26±0.43

F4	98.16±1.07	45±0.75	35±0.76
F5	99.72±0.98	30±0.54	30±0.45
F6	99.47±0.65	30±0.55	25±0.76

TABLE: 9 DISSOLUTION PROFILE USING CROSPROIDONE SUPERS DISINTEGRATING AGENT.

% DRUG RELEASE			
Time Min	F-1	F-2	F-3
0	0	0	0
2	30.79 ±0.983	35.08±0.549	36.67±0.223
4	35.08±0.983	40.84±0.654	56.63±0.836
6	40.99±0.983	46.63±0.863	62.89±0.256
8	45.08±0.746	55.89±0.763	74.67±0.435
10	51.84±0.983	62.67±0.588	78.69±0.983
12	56.63±0.549	67.69±0.345	83.99±0.756
14	62.89±0.749	76.99±0.123	89.00±0.753
16	68.67±0.983	91.62±0.983	91.67±0.529
18	72.69±0.663	95.67±0.756	95.85±0.223
20	76.99±0.943	99.85±0.356	96.99±0.742
22	82.00±0.756	99.99±0.123	
24	88.67±0.976		
16	92.85±0.223		
28	95.99±0.967		
30	98.93±0.234		

TABLE: 10 DISSOLUTION PROFILE USING SSG SUPERS DISINTEGRATING AGENT .

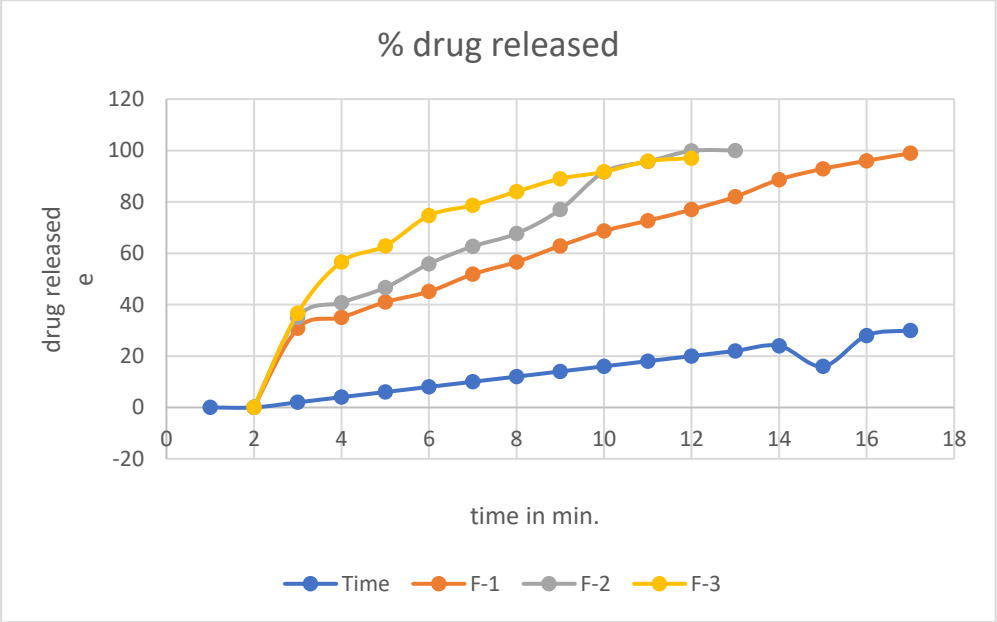

fig 6 dissolution profile using crosproidone supers disintegrating agent .

% DRUG RELEASE			
Time Min	F-4	F-5	F-6
0	0	0	0
2	30.79±0.549	40.99±0.345	45.08±0.983
4	35.08±0.549	45.08±0.987	51.84±0.643
6	40.99±0.345	51.84±0.224	56.63±0.345
8	45.08±0.353	56.63±0.345	62.89±0.567
10	51.84±0.756	62.89±0.347	68.67±0.353
12	56.63±0.356	68.67±0.876	72.69±0.549
14	62.89±0.396	72.69±0.356	76.99±0.348
16	68.67±0.983	76.99±0.549	84.09±0.388
18	72.69±0.549	82.01±0.563	88.67±0.765
20	76.99±0.673	88.67±0.674	89.99±0.353
22	81.01±0.674	92.85±0.345	95.02±0.549
24	88.67±0.387	96.02±0.345	99.03±0.876
26	92.85±0.347	99.97±0.123	99.99±0.734
28	95.99±0.345		
28	99.98±0.876		

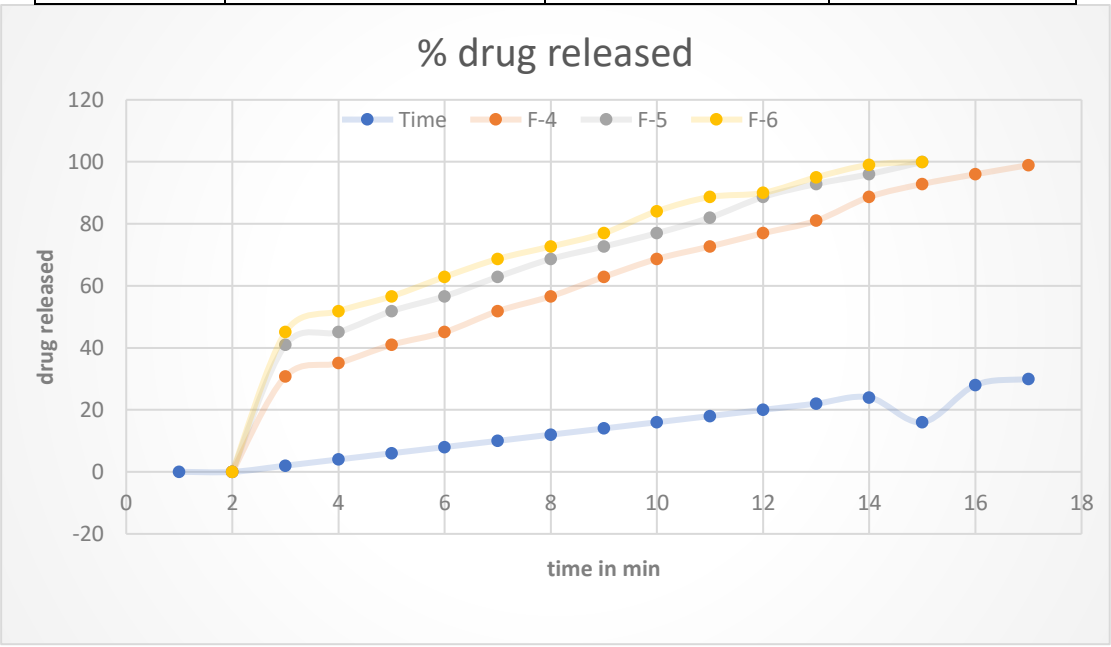

Fig : 7 Dissolution profile using (SSG)sodium starch glycolate supers disintegrating agent.

Result: this research was based on formulation and optimization Solid dispersion method enhances solubility by dispersing poorly soluble drugs in a solid matrix, such as a polymer, increasing their surface area and promoting dissolution, thus improving bioavailability and formulation properties. And use water soluble carrier poloxamer 188, poloxamer 407, PEG 4000,PEG 6000 in different ratio loke 1:1,1:2,1:4and 1:6 and evaluation after formulation of solid dispersion physical appearance ,drug

lodging ,solubility and drug released and it was found F11 formulation show optimized result so F 11 formulation of solid dispersion are in dispersible tablet preparation in which super disintegrating agent use Crosproidone and SSG indifferent ratio 10,15and 20 mg use and formulate dispersible tablet by direct compression method and after formulation dispersible table and evaluation of precompression and post compression evaluation parameter perform it was conformed .

Conclusion: The research study described was focused on formulating and optimizing solid dispersions to enhance the solubility of poorly soluble drugs. Solid dispersion is a technique that involves dispersing such drugs in a solid matrix, typically a polymer, to increase their surface area and promote dissolution. This approach improves the bioavailability and formulation properties of these drugs. In the study, water-soluble carriers like poloxamer 188, poloxamer 407, PEG 4000, and PEG 6000 were used in different ratios (1:1, 1:2, 1:4, and 1:6) to prepare the solid dispersions. After optimized SDF11 formulation are use tablet formulation by direct completion method After the evaluation process, it was confirmed that the F2 formulation showed the best results among the dispersible tablet formulations.

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