www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2016; 5(7): 08-12
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www.thepharmajournal.com
Received: 01-05-2016
Accepted: 02-06-2016

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Enhancement of drug dissolution of glibenclamide using solid dispersion technique

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Abstract
The term solid dispersion refers to a group of the solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug and matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Solid dispersion technologies are particularly promising for improving the aqueous solubility, dissolution rate and bioavailability of BCS Class II drugs as bioavailability of drugs depends on their solubility and permeability. The main objective of the present work was to evaluate the feasibility of the melt granulation technique to improve the dissolution characteristics of a poorly water soluble drug, Glibenclamide. Glibenclamide was chosen as a water-insoluble model drug. Conjugation of Glibenclamide with the different types of carriers was used to increase its Solubility and dissolution rate. Formulation of granules was done by physical mixture and melt granulation technique. The drug carrier interactions were studied by IR spectral analysis. Granules were evaluated by Bulk density, Tapped density, Carr's index, Hausner ratio and Angle of repose. *In-vitro* dissolution studies were done on solid dispersion formulations.

Keywords: Solid Dispersion, Glibenclamide, Melt Granulation

Introduction
Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight, composition, drug crystalline, particle porosity and wet ability, when successfully controlled can produce improvements in bioavailability [1]. In solid dispersions there is dispersion of one or more active ingredients in an inert matrix where the active ingredients exist in finely crystalline, solublised or amorphous state and used to enhance the solubility and oral bioavailability [2]. A griseofulvin-inpoly (ethylene glycol) solid dispersion (Gris-PEG, Novartis) and a nabilone-in-povidone solid dispersion (Cesamet, Lilly) were marketed during three decades following the initial work of Sekiguchi *et al.* in 1961 [3].
Solid dispersion is more acceptable technique for improving solubility than other techniques due to its applicability, effectiveness and ease of production. Salt formation technique is only applicable for solubility enhancement of weakly acidic or basic drugs and not effective for neutral drugs. *In vivo*, it converts into their respective acidic or basic forms which leads to reduction in bioavailability [4, 5]. Solubilisation technique is more indicative for the preparation of liquid formulation but not the solid dosage forms so lack patient acceptability. Particle size reduction can be achieved only up to a certain limit which is not acceptable for improved solubility as the more powder form have difficulty in handling, decreased mechanical strength and poor flow [6].

Melt Granulation Technique
This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, solid dispersion is prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration because these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate

size, agglomerate size distribution and densification of agglomerates [7, 8].

Materials and Methods

Preparation of Granules

Melted granules were prepared in a porcelain dish. Firstly, the mixture of FNO with hydrophilic polymer (Polyethylene glycol) or surfactant (poloxamer-188) mentioned in Table-1 was dry blended for 10 min. Then, this mixture was placed in hot porcelain dish and supply the heat around 60^0C on temperature controlled water bath so as to melt the polymers or surfactant in which the drug was dispersed. The formed melted mass is then cooled to room temperature and at the end of the granulation process the granules were allowed to solidify at room temperature by spreading them in thin layers on glass plates. Pass the melted dried granules through sieve no # 20 so as to form uniform granules. The cooled granules were stored in sealed bags for their evaluation. Prepared the physical mixtures of the same formulation and compared the solubility and dissolution rate with the melt granules.

Table 1: Product coding and solid dispersions with polymer and surfactant.

Sr. No.	Composition	Drug: Excipient Ratio	Coding
1.	Glibenclamide		GLI
2.	Melt Granules		
2A	Glibenclamide:PEG	1:1	GLI:PEG1
2B	Glibenclamide:PEG	1:2	GLI:PEG2
2C	Glibenclamide:PEG	1:3	GLI:PEG3
2D	Glibenclamide:Poloxamer	1:1	GLI:POL1
2E	Glibenclamide:Poloxamer	1:2	GLI:POL2
2F	Glibenclamide:Poloxamer	1:3	GLI:POL3
3.	Physical Mixture		
3A	Glibenclamide:PEG	1:1	GLI:PEG1(PM)
3B	Glibenclamide:PEG	1:2	GLI:PEG2(PM)
3C	Glibenclamide:PEG	1:3	GLI:PEG3(PM)
3D	Glibenclamide:Poloxamer	1:1	GLI:POL1(PM)
3E	Glibenclamide:Poloxamer	1:2	GLI:POL2(PM)
3F	Glibenclamide:Poloxamer	1:3	GLI:POL3(PM)

Results and Discussion

Preformulation Studies

Drug characterization

Glibenclamide was found to be white colored powder with no odor. The melting point of Glibenclamide was found to be 174 ^{0}c by capillary fusion method. The partition coefficient of Glibenclamide was determined using octanol/water system by shake flask method and was found to be 4.70. The absorption maximum (λ max) of the drug was found by using double beam UV spectrophotometer and it was found to be 229 nm.

FT-IR Spectroscopy

The infrared spectrum of Glibenclamide (Figure-1) confirms the presence of the relevant functional group (as the important peaks are listed in Table-2) is compared with the literature.

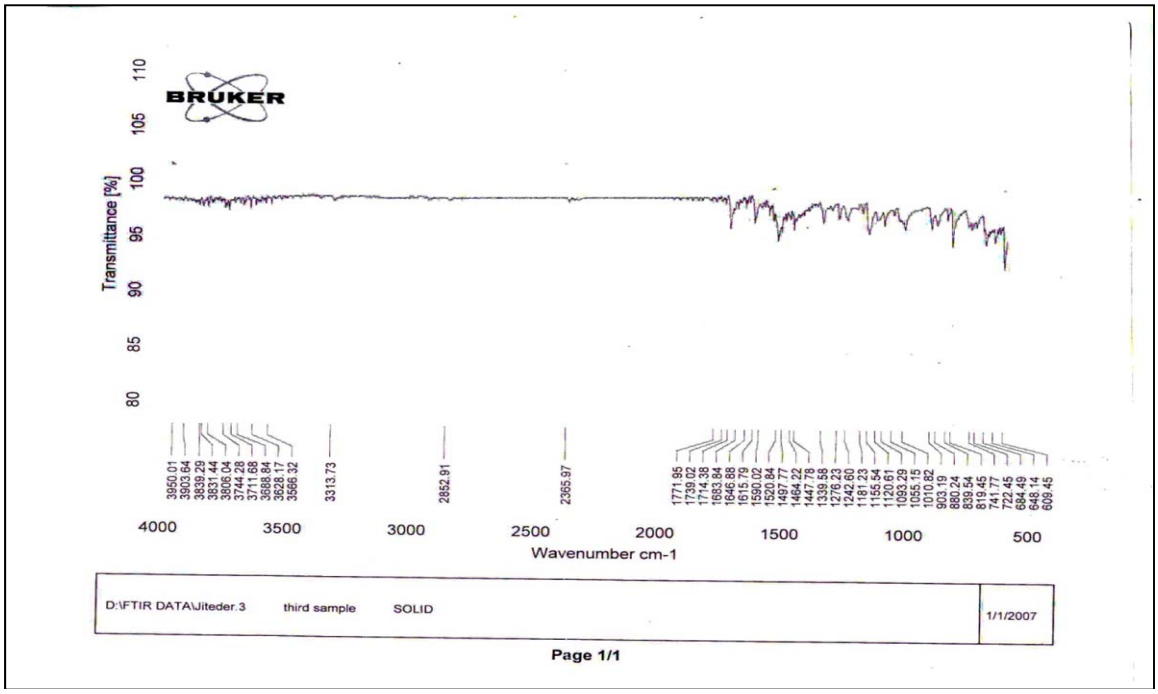

Fig 1: FT-IR spectrum of Glibenclamide

Table 2: Interpretation of FTIR Spectrum of Glibenclamide

Reference peak (cm^{-1})	Observed peak(cm^{-1})	Functional group (Vibration)
600-800	684.9	Cl (Stretching)
3000-3700	3688,3628	NH (Stretching)
1600-1900	1771,1739	C=0 (stretching)
1715	1714	OCH3 (stretching)
1060	1055	S=0

Drug Polymer interaction study

Drug excipient studies showed that there was no discoloration, liquefaction between drug and polymer. FTIR spectra of the physical mixture of drug and polymer showed no physical interaction between drug and the polymer used. No significant shift in the peak was observed which revealed that both the drug and polymer are compatible with each other.

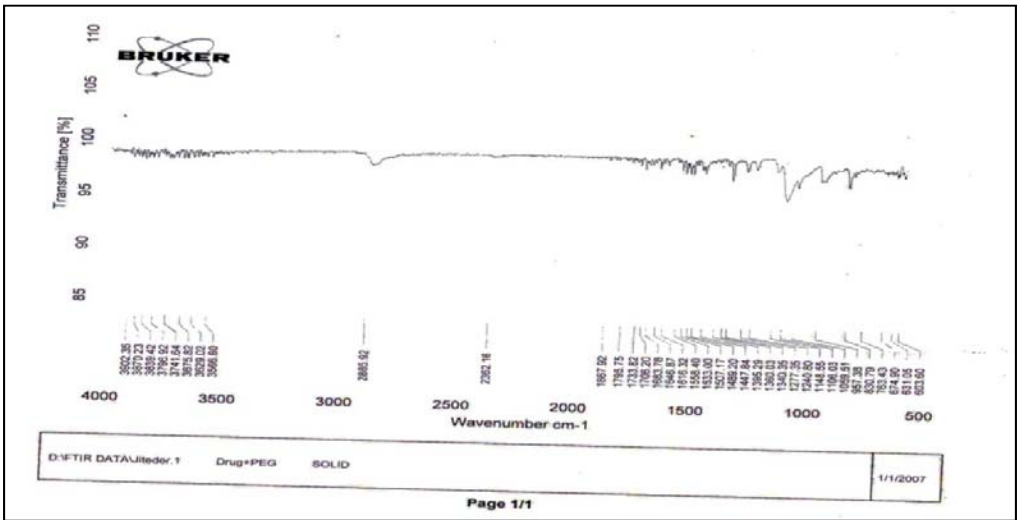

Fig 2: IR Spectra of Mixture Drug and PEG 6000

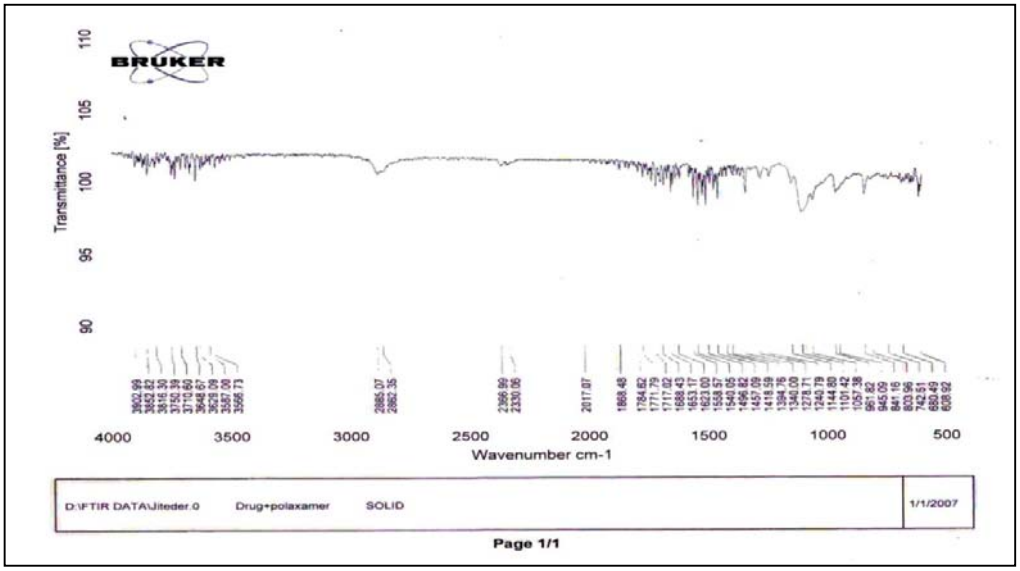

Fig 3: IR Spectra of Mixture Drug and Poloxamer 188

Determination of percentage yield of granules

Table-3 shows the percentage yield of the granules recovered. It was found that the percentage practical yield got increased as the amount of polymer added to the formulation increased, although it may not be depend on drug concentration in the formulation.

Table 3: Percentage yield of granules

Sr. No.	Formulation code	Percentage yield
1	GLI:PEG1	69.3
2	GLI:PEG2	52.6
3	GLI:PEG3	56.5
4	GLI:POL1	44.5
5	GLI:POL2	64.6
6	GLI:POL3	40.6

Table 4: Characterization of Blends

Parameters					
Parameters Formulation	**Bulk Density (g/cc)**	**Tapped Density (g/cc)**	**Hausners Ratio**	**Compressibility Index (%)**	**Angle of Repose(o)**
GLI:PEG1	0.614 ± 0.002	0.564 ± 0.003	1.236 ± 0.0007	13.00 ± 0.05	24.418 ± 1.09
GLI:PEG 2	0.460 ± 0.002	0.464 ± 0.003	1.170 ± 0.0008	12.075 ± 0.06	17.797 ± 1.21
GLI:PEG 3	0.407 ± 0.002	0.555 ± 0.003	1.134 ± 0.0007	12.841 ± 0.05	22.976 ± 0.99
GLI:POL 1	0.488 ± 0.002	0.563 ± 0.002	1.130 ± 0.0005	10.972 ± 0.04	24.132 ±1.53
GLI:POL 2	0.440 ± 0.002	0.490 ± 0.020	1.061 ± 0.048	12.370 ± 4.27	19.412 ± 1.17
GLI:POL 3	0.564 ± 0.002	0.648 ± 0.002	1.209 ± 0.0005	9.50 ± 0.04	20.412 ± 1.23

Granule Size Analysis

Particle size of granules was determined by optical microscopy method. Optical microscopy method of all formulation were used to determine the average particle size of granules.

Average particle size range was found to be 72-190µm.

Determination of Drug Content

Drug Content = (Practical Drug Conc. / Theoretical Drug Conc.) ×100

Table 5: Percent Drug Content of Glibenclamide PEG 6000, Poloxamer188 Solid Dispersions

Formulation Number	% Drug content
GLI:PEG1	95.2946 ± 3.836
GLI:PEG2	92.068 ± 1.767
GLI:PEG3	89.1353 ± 0.878
GLI:POL1	94.8554 ± 0.391
GLI:POL2	98.060 ±1.507
GLI:POL3	96.0104 ± 2.191

***In vitro* Drug Release Studies**

Accurately weighed physical mixtures and solid dispersions equivalent to 8mg of Glibenclamide were added to 900 ml of dissolution medium in USP II Paddle type apparatus and stirred at a speed of 50 rpm at 0.5℃.5ml dilution were withdrawn at 0, 5, 10, 20, 30, 45, 60 minutes and replaced by 5 ml of fresh dissolution media. The collected samples were analyzed after filtration and dilution at 255 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution studies of pure Glibenclamide were performed similarly. The release profile data was analyzed for cumulative percent drug released at different time intervals. The dissolution profile of pure drug, physical mixture and solid dispersion were carried out in 0.1N HCl. The presence of Poloxamer188 and PEG 6000 increases the dissolution of Glibenclamide from the solid dispersion, which increases the dissolution rate as shown in Figure- 4 and Table-6.The figure indicates that the solid dispersion GLI:POL5 gives fastest dissolution of drug as compared to other formulation. Solid dispersion technique has improved the dissolution rate of Glibenclamide to greater extent.

Table 6: Dissolution Release Profile of Solid Dispersion Formulations

Time (min)	GLI:PEG1	GLI:PEG2	GLI:PEG3	GLI:POL1	GLI:POL2	GLI:POL3
0	0 ± 1.76	0 ± 0.29	0 ± 1.72	0 ± 1.34	0 ± 2.07	0 ± 0.29
5	7 ± 3.06	8.43 ± 2.99	5.21 ± 1.73	11.25 ± 1.75	6.00 ± 0.53	10.89 ± 0.17
10	23.89 ± 1.78	22.11 ± 0.44	24.94 ± 0.58	25.45 ± 2.64	24.37 ± 0.36	24.45 ± 0.31
20	38.74 ± 1.08	36.940 ± 0.37	40.25 ± 0.28	41.54 ± 2.40	40.33 ± 0.16	45.28 ± 0.18
30	50.13 ± 0.29	52.45 ± 0.31	56.114 ± 0.16	60.12 ± 0.68	63.88 ± 0.21	61.54 ± 0.46
45	61.74 ± 0.74	67.94 ± 0.17	62.42 ± 0.19	69.43 ± 0.63	77.221 ± 0.33	72.43 ± 0.49
60	71.69 ± 0.02	74.5 ± 0.20	73.84 ± 0.28	81.31 ± 0.65	85.11 ± 0.27	82.58 ± 0.07

In vitro drug release of optimized formulation and comparison with marketed tablets

Table 7: Cumulative % Drug Released Data

Time (min)	Cumulative %Drug Released of Optimized Formulation	Cumulative % Drug Released of Marketed Tablets
5	6	2
10	24.37	8.11
20	40.33	20.25
30	63.88	43.66
45	77.22	64.00
60	85.11	75.33

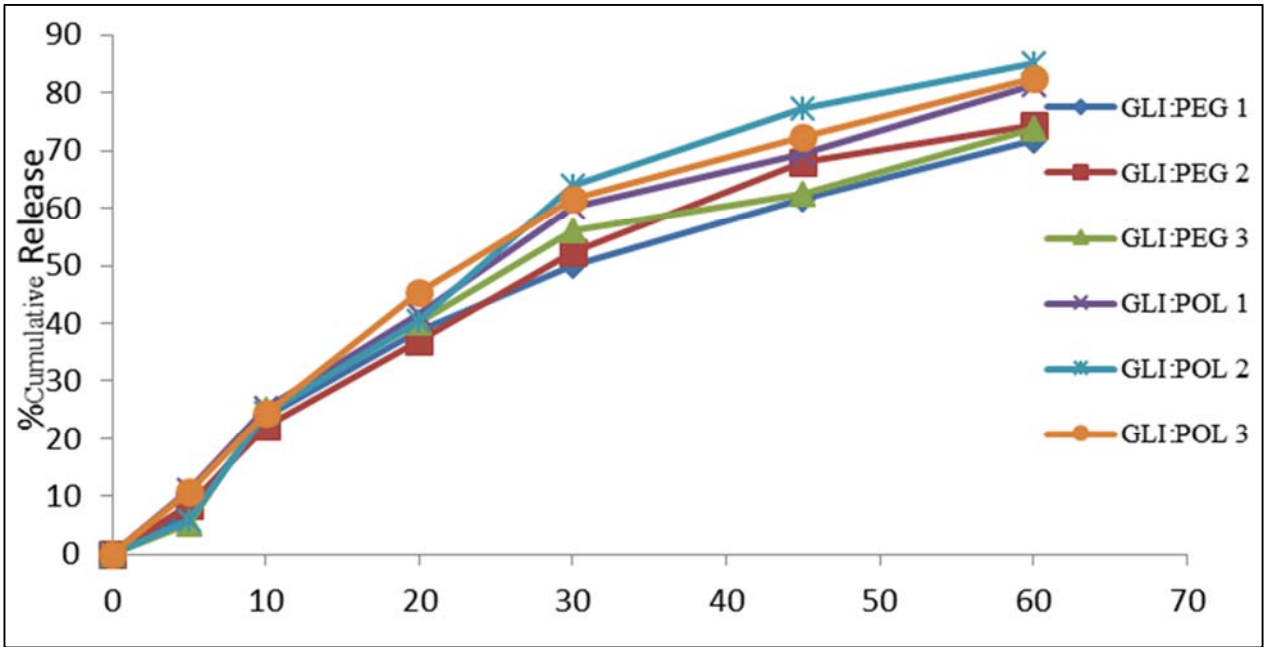

Fig 4: Cumulative% Drug Released Curve of Solid Mixture

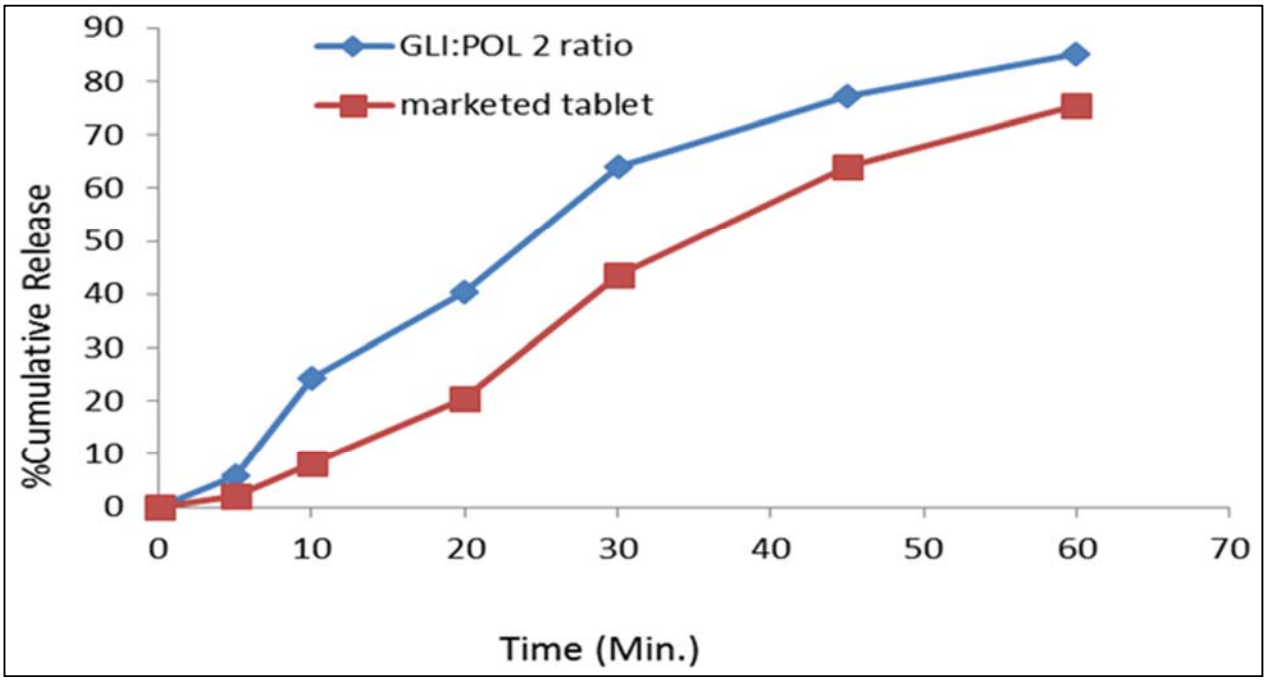

Fig 5: Cumulative % Drug Released Curve of Optimized poloxomer1:2 and Marketed tablet

Conclusion

Melt granulation technique has been proved to be a important process to increase the solubility, dissolution and other technique characteristics of Glibenclamide using PEG and Poloxamer as a melt binder, without using any solvents. Percentage practical yield was found to be maximum in formulation GLI: POL 2. Particle size analysis by optical microscopy of the granules revealed that the particles were in micron range. *In-vitro* release study indicated that the melt granule of GLI:POL2 gives fast dissolution rate 85.11% of drug as compared to other polymers Solid state analysis indicated slightly reduction in crystalline form of the drug and no changes in its polymorphic form. The granules displayed significant improvement *in vitro* drug dissolution behaviour. There are no interaction between drug and excipient. Glibenclamide and Poloxamer solid dispersion in 1:2 ratio revealed better solubility and dissolution rate and this formulation has been selected for *in vitro* dissolution study compared with marketed formulation GLI: POL2 exhibit better release (85.11%) that is over marketed formulation (75.33%) in 60 min.

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