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Research Article

Formulation and Evaluation of Poorly soluble drug Josamycin by Solid Dispersion

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ABSTRACT
The objective of the present work is to mask the intensely bitter taste of Josamycin and to formulate an FDT of the taste-masked drug by incorporation of Excipients in the tablets. Method of Josamycin was prepared by solvent evaporation method using methanol as solvent for pH-sensitive polymer: act as the encapsulating medium. The Mixture of Josamycin with PEG 6000 indicates highest increase in solubility with 3.7-folds Josamycin and PEG 6000 (1:2SD) were selected as optimized combinations for Josamycin. The optimized combinations was formulated into Fast dissolving tablet. The optimized combinations were subjected to FT-IR and while dissolution, and accelerated stability studies were performed on their formulations. The physical properties were evaluated with regard to yield, drug content, flow properties, particle size, in vitro drug release and taste. The average size of microspheres was found to be satisfactory in terms of the size and size distribution. The FDTs prepared by direct compression method and evaluated for hardness, thickness, weight variation, friability, disintegration time, drug content, wetting time, in vitro disintegration, in vitro drug release and stability. Result and discussion simulated salivary fluid (pH 6.8) and sufficient flow properties was shown in the drug: polymer ratio.

Key Words: Taste Masking, Josamycin, Fast dissolving tablet, superdisintegrants.

INTRODUCTION
Orally administered drugs completely absorbed only when they show fair solubility in gastric medium and such drugs shows good bioavailability. In recent times more than 40 % NCEs (New Chemical Entities) developed in Pharmaceutical Industry are practically insoluble in water. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. [1,2]

Taste and its physiology
Phsiysiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue . The sense of taste is conducted to the brain by a process called taste transduction. Human have around 10,000 taste buds which appear in fetus at about three months.
The poor solubility of drug substances in water and their low dissolution rate in the aqueous gastro-intestinal fluids often lead to insufficient bioavailability. According to the equation of Noyes and Whitney, this may be achieved by an increase in the surface area of the drug which is accessible for the dissolution medium of the stomach. The gelation was takes place after the orally administered solution reached the stomach by complexing the calcium with sodium. [2]

MATERIALS AND METHODS
Materials
Josamycin was obtained from Symbiosis pharmaceutical, H.P, Sodium CMC, Aspartame, MCC,PEG 600,all are of analytical grade.

Methods
Determination of maximum absorbance (λ max)
Stock solutions (100μg/ml) of Josamycin were prepared in methanol. These Solutions were diluted with methanol to obtain suitable concentrations of each. The UV spectrums were recorded in the range 200-450 nm by using UV-Visible double beam spectrophotometer (Shimadzu 2450). The wavelength of maximum absorption (λ_{max}) was determined [7].

Differential Scanning Calorimetry study of Josamycin
DSC analysis was performed using Shimadzu-Thermal Analyzer DSC 60 on 2-5mg samples. Sample was heated in an open nitrogen pan at a rate of 10°C/min conducted over a temperature range of 116 to 125°C for Josamycin under nitrogen flow of 2 bar pressure.

Formulation of Solid Dispersion
The solid dispersion was prepared by using PEG6000 as a hydrophilic carrier.
Different drug and polymer ratios were employed

in different ratios & SD's were prepared by Solvent evaporation method.

Solvent Evaporation (SE) method:
Solid dispersions were prepared using a SE method. Drug & polymers (PEG 6000)were dissolved in methanol in different ratio & the solution were made homogeneous by continuous stirring and solvent was evaporated by subjecting the solution with constant stirring at 70 to 80°C till complete evaporation of solvent. The obtained SD's were dried and subsequently pulverized by triturating in pestle-mortar and screened through 60 mesh sieve.

Method of Preparation of Powder Blend
Josamycin : PEG 6000 and other inactive ingredients along with varying % of sodium starch glycolate, Croscarmellose sodium, Crospovidone at three concentration levels. Formulations coded as F1 to F9 respectively. In the first step, active and inactive ingredients weighed accurately and were screened through a 60-mesh sieve. The complex (Josamycin:PEG 6000) and super disintegrants were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 20 min. Finally the blend is passed through mesh #40 and used for evaluation of flow characteristic. Formula for Fast Dissolving tablet of Josamycin.

Table 1 : Formula for fast dissolving tablet of Josamycin

Ingredients	Formulation code								
Quantity(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Josamycin equivalent to 150mg	250	250	250	250	250	250	250	250	250
Crospovidone	8	8	8	10	10	10	12	12	12
Sodium Starch glcolate	8	10	12	8	10	12	8	10	12
Mannitol	80	75	75	75	80	75	75	75	70
Magnesium stearate	2	2	2	2	2	2	2	2	2
Micro Crystalline Cellulose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total Weight (mg.)	350	350	350	350	350	350	350	350	350

Post-compression Evaluation of Fast Dissolving tablet Thickness
The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier Calliper. Three tablets were used.

Hardness
The hardness of three tablets was checked using the Monsanto hardness tester (LAB- HOSP)

Drug content (Assay)
Twenty tablets were weighed individually and powdered. The powder equivalent to 10 mg of Josamycin was weighed and dissolved in 6.8 pH buffer. The volume was made to 100 ml with 6.8 pH buffer. From this stock solution, 10 μg/ml dilutions were prepared. The drug contents of the resulting solution were calculated from UV absorbance at 205.[5]

Friability
Friability is the measure of tablet strength. In this test number of tablets subjected to combined effect of shock abrasion by utilising a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche Friability tester This was then operated for 100 revolutions. The tablets then dedusted and reweighed. Permitted friability limit is 1.0%. Tablets were then weighed and friability values were determined.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} X\ 100$$

where
W_1 = weight of the tablets before test,
W2 = weight of the tablets after test.

Weight Variation
Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (7.5%). The Percent deviation was calculated using the following formula.[6]

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Table 2 : Standard Values of Weight Variation

Sr. No.	Average weight of tablets (mg)	Maximum percent deviation allowed (%)
1	80 or less	10
2	More than 80 but less than 250	7.5
3	More than 250	5

Wetting Time

A piece of tissue paper folded double was placed in a petri dish containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0 C. A method was used to measure wetting time and capillarity of the FDT.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in small Petri dish (7.5cm) containing 7ml water. A tablet was put on the tissue paper and allows wetting completely. The wetted tablet was then weighed. The water absorption ratio R was determined using following equation.

$$R = \frac{W_a - W_b}{W_a} X\ 100$$

where

W_a = weight of a tablet after absorption

W_b = weight of a table before absorption

Disintegration Time Study

The in-vitro disintegration studies were carried out using Tablet Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube.

In- vitro Drug Release Study

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally.

Apparatus: 2 (Paddle)
Medium: 900 ml of 0.07 N HCL.
Speed: 55 rpm.
Times: 1, 5, 7, 9, 10, 13 and 15min.
Temperature: 37^0c.
One Tablet was placed in jar containing 900ml of 0.07N HCl. At different time interval specified (1, 3, 5, 7, 9, 11, 13 and 15 min) 10 ml of aliquots were withdraw then filtered through whatman filter paper no.52. Cumulative percentage of labelled amount of drug released was calculated. The drug release was compared with positive control (Placebo for Josamycin).[11]

Stability Studies

The optimized formulation was wrapped in aluminum foil and subjected to 40 ±2°C temperature and 75±5% RH in oven for the period of Six months. The formulation was analyzed for hardness, drug content, Disintegration time, and dissolution.

Packaging material

The tablets were wrapped in aluminum foils.

Sampling points

The optimized formulations were subjected to stability for a period of Three months. The samples were withdrawn at the end of Six months.

RESULTS AND DISCUSSION

Preformulation Study

Table 3: Results Of Organoleptic Properties Of Josamycin

Drug	Properties	Observed Result
Josamycin	Appearance	Crystalline powder
	Colour	White
	Odour	Odourless

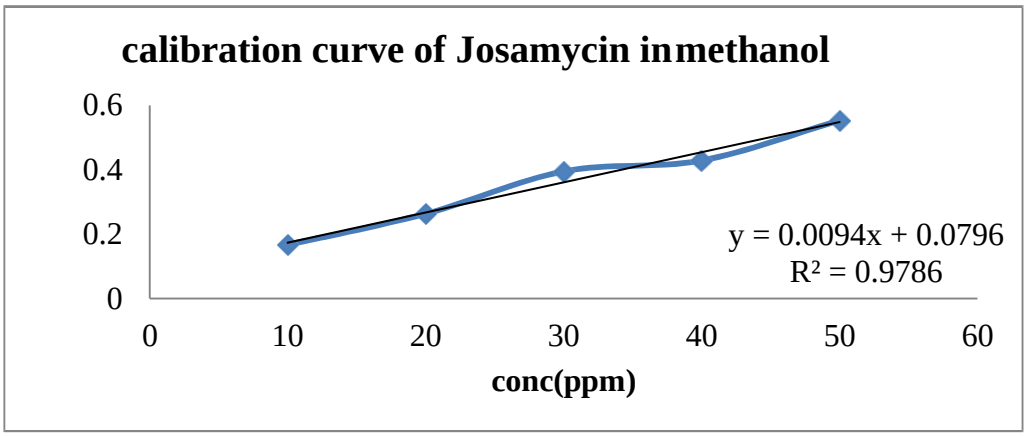

Fig 2 :Calibration Curve of Josamycin in methanol

Solubility Study of Josamycin

Table 4: Solubility Profile Josamycin

Sr. no.	Solvent
1	Methanol
2	Phosphate buffer pH 6.8
3	Phosphate buffer pH 6.0

Compatibility study FTIR

Major functional groups present in Josamycin show characteristic peaks in IR spectrum. shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks were identical to functional group of Josamycin. Hence, the purity of sample was confirmed.

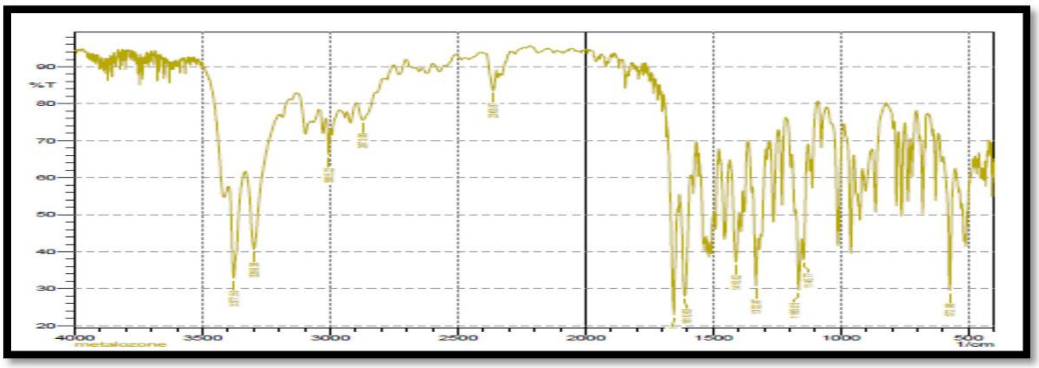

Fig 3: FT-IR. Spectrum of Josamycin

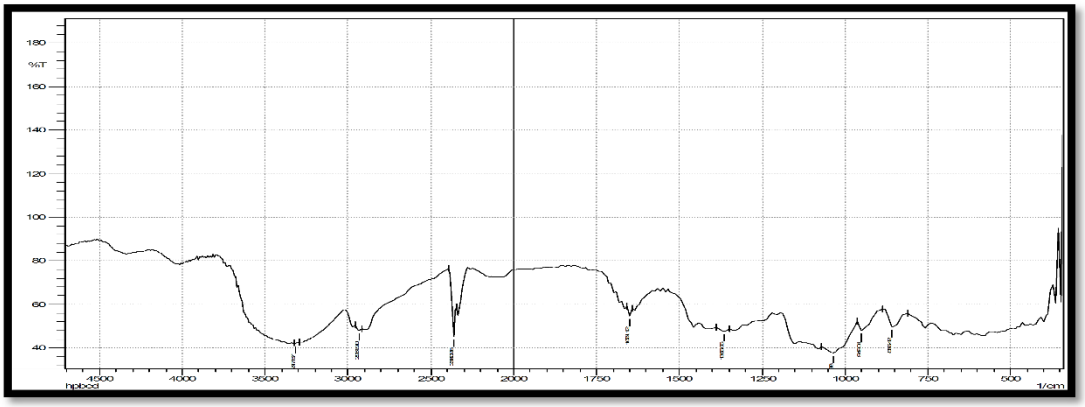

Fig 4: FT-IR study of Drug+Crosspovidone+excipient mixture

The presence of absorption bands corresponding to the functional groups N-H Streching pri, sec amine 3377cm^{-1}, O- H Streching carboxylic acid 3299 cm^{-1}, C=C Streching alkenes 1664 cm^{-1} C-C stretching aromatics 1410 cm^{-1} C-N Streching aromatic amine1332 cm^{-1}, C-O Streching carboxylic acid 1165 cm^{-1},present in the structure of Josamycin and the absence of any well-defined unaccountable peaks is a confirmation of the purity of the drug sample. From above spectrum, it was found that Josamycin is compatible mixture of all excipient.

Phase Solubility Study

The prepared SD's were subjected for solubility study to evaluate the effect of different carriers on the aqueous solubility of RXM and results of solubility analysis The aqueous solubility of RXM was found to be 0.0832 mg/ml. The aqueous solubility of a drug, less than 0.1 mg/ml often present dissolution limitation to absorption. From the result of phase solubility analysis it can be clearly established that the carriers like PEG 6000 and are having very good solubility enhancing property.

Table 5: Summary of Josamycin PEG 6000 Phase Solubility Studies

Cyclodextrin/ medium	Phase solubility diagram	Stability constant M^{-1}	Increased solubility S_t / S_o	Complexation Efficiency
PEG 6000 in distilled water	AL	162.5	3.72	0.042

X-Ray diffraction

The X-ray diffraction pattern Mixtures prepared by Solid dispersion

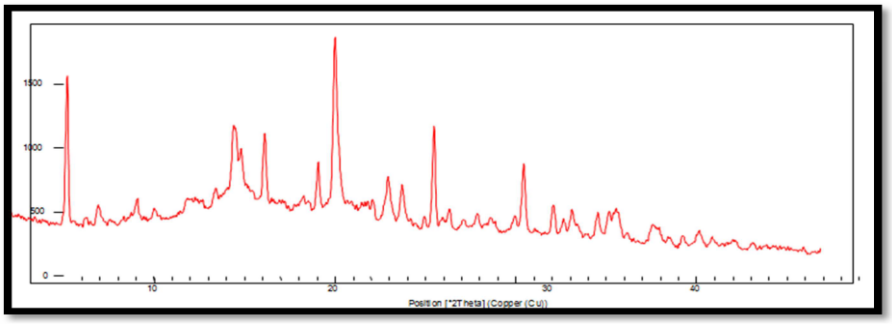

Figure 5: XRD of Solid dispersion (1:2)

From the Fig X-ray diffracometry (XRD) spectra Drug. The x-ray diffractogram of Josamycin has sharp peaks at diffraction angles (2θ) 12.26-, 15.88-, 19.88-, 22.08-, and 23.92- showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of both physical mixtures and solid dispersion system.[12]

Differential scanning calorimetry

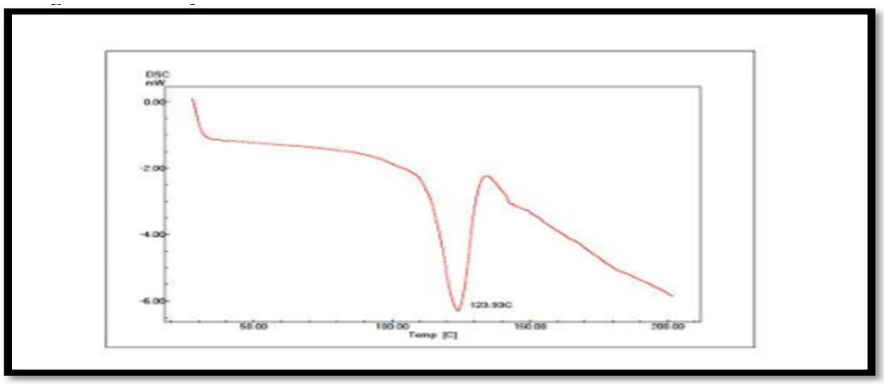

Figure 6 : DSC study of Josamycin

The DSC curve of Josamycin profiles a sharp endothermic peak at 123°C corresponding to its melting, which confirm the purity of the drug. The drug do not undergoes decomposition following its melting.

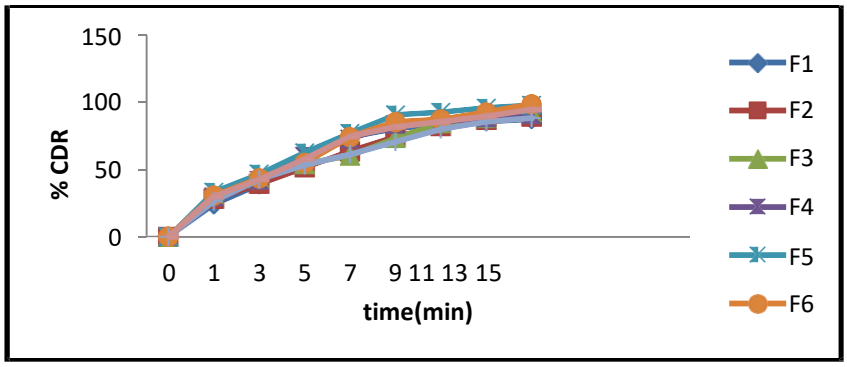

Figure 7: Dissolution profile of fast dissolving tablets of Josamycin

Percent drug release data expressed Indicate In-Vitro release study was shown 98.7% release of Josamycin through F6 formulation in 15 minutes. Formulation F6 showed less disintegration time and percent cumulative drug release 98.7% so it was declared as an optimized formulation and was subjected for further evaluation and stability studies.

Table 6: Evaluation Parameters Of F6 Optimized Batch

Sr. No.	Parameters	Results*
1	Weight variation (mg)	98.30 ±1.90
2	Thickness (mm)	3.8 ± 0.05
3	Hardness (kg/cm^2)	2.17 ± 0.28
4	Friability (%)	0.72 ± 0.05
5	Wetting time (sec)	67.66 ± 3.51
6	Disintegration time (sec)	61.66 ± 2.51
7	Uniformity of content (%)	98.46 ± 1
8	Water absorption ratio(%)	58.28 ± 6.26

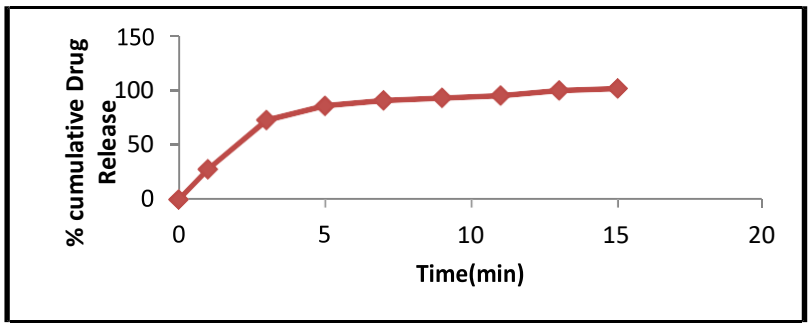

Figure 8: Graphical presentation of dissolution profile of optimized batch

Table 7: Parameters Studied Of [F6] Formulation Before And After Stability Study

Parameters	Before stability study	After stability study
Colour	White	White
Thickness (mm)	3.87 ± 0.05	3.67 ±0.20
Hardness (kg/cm^2)	2.17 ± 0.28	2.67 ± 0.28
Content uniformity (%)	98.46 ± 1	97.66 ± 1.15
Weight variation(mg)	99.73 ± 1.90	99.73 ± 1.90
friability (%)	0.72 ± 0.05	0.74±0.5
Disintegration time (sec.)	61.66 ± 2.51	62.33 ± 2.08
Wetting time (sec.)	68± 2	66.67 ± 1.52
Water absorption ratio (%)	58.27 ± 6.26	57.54 ± 6.21

Stability Study

The accelerated stability study was carried out on optimized formulation F6. The tablets were wrapped in aluminium foil and stored at 40 ± 2^0C &75 ± 5 % RH for a six months. After three months samples were withdrawn and tested for physical parameters, thickness, hardness, percent friability, content uniformity, disintegration time, wetting time, Water absorption ratio (%) and in-vitro drug release studies.[8]

Table 8: Dissolution Study of Formulation [F6] Before And After Stability Study.

Time (min)	% Cumulative Drug release	
	Before S.S.	After S.S.
1	27.67 ± 1.53	28.43 ± 1.14
3	72.53 ± 10.28	56.34 ± 1.05
5	85.54±12.70	72.22 ± 2.89
7	90.46±9.93	76.72±1.56
9	92.84±8.16	84.67 ±1.22
11	94.87±6.62	96.43 ± 0.11
13	99.57±3.14	98.11 ± 0.67
15	101.38 ±2.48	100.21 ±2.03

CONCLUSION

Josamycin slightly soluble in water. According to the biopharmaceutical classification, it comes under Class IV and its poor aqueous solubility and dissolution is rate-limiting step in the absorption of poorly water soluble drug.

Oral bioavailability of Josamycin can be improved by using the Solid dispersion technique. The prepared combinations were characterized by FT-IR, DSC, XRD, dissolution study.

Based on the results of saturation solubility studies The Mixture of Josamycin with PEG 6000 indicates highest increase in solubility with 3.7-folds Josamycin and PEG 6000 (1:2SD) were selected as optimized combinations for Josamycin. The optimized combinations was formulated into Fast dissolving tablet. The optimized combinations were subjected to FT-IR and while dissolution, and accelerated stability studies were performed on their formulations.

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