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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF METHADONE ORO DISPERSIBLE TABLETS

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ABSTRACT

In the present work, an attempt has been made to develop fast disintegrating tablets of Methadone. In the present work Sodium starch glycollate, Cross povidone and Cross carmellose sodium were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. Camphor was employed as sublimating agent, due to presence of camphor maximum pores will be formed. As the number of pores were more the body fluid will penetrates more easily. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 98.78 % in 8 min hence it is considered as optimized formulation. The F4 formulation contains Cross Povidone as super disintegrate in the concentration of 12 mg.

Key words: Methadone, Camphor, Odium Starch Glycollate , Cross Povidone, Cross Carmellose Sodium.

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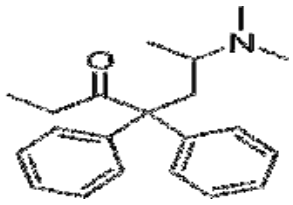
INTRODUCTION

Drug Profile

Drug name: Methadone
Synonyms: dl-Methadone, Methadonum
Category: Analgesics, Opioid, Narcotics, Antitussive Agents
Structure:



Description : A synthetic opioid that is used as the hydrochloride. It is an opioid analgesic that is primarily a mu-opioid agonist. Methadone is also used as part of the treatment of dependence on opioid drugs, although prolonged use of methadone itself may result in dependence.
CAS NO: 76-99-3
IUPAC name: 6-(dimethylamino)-4,4-diphenylheptan-3-one
Molecular formula: C21H27NO
Molecular weight: Average: 309.4452 Monoisotopic: 309.209264491g/mol.
Solubility: Very soluble in ethanol
Melting point: 235.0 °C
Bioavailability: 36 to 100%
Half-life : 24-36 hours
Protein binding: In plasma, methadone is predominantly bound to α1-acid glycoprotein (85% to 90%).
Dosage forms and Dose: tablets-1,5,10,25mg.

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Mechanism of Action

Methadone is a mu-agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe. Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Cross Carmellose Sodium

Chemical Name and CAS Registry Number:

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

Functional Category: Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Cross Povidone

Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Functional Category: Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Sodium Starch Glycollate

Chemical Name and CAS Registry Number:

Sodium carboxymethyl starch [9063-38-1]

Functional Category: Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct- compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

MATERIALS AND METHODS

Preformulation Studies

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

Determination of absorption maximum (λ_{max})

Absorption maximum is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Methadone was weighed accurately 10 mg and transferred to 100 ml volumetric flask, dissolved in phosphate buffer pH 6.8 and the final volume was made up to 100 ml with phosphate buffer pH 6.8 to get a stock solution (100µg/ml). From the stock solution, 1 ml was pipette out in 10 ml volumetric flask and the final volume was made up to 10 ml with phosphate buffer PH 6.8 to get 10µg/ml. Then this solution was scanned at 200-400nm in UV-Visible double beam spectrophotometer (UV-3200, Labindia, India) to get the absorption maximum (λ_{max}).

Flow properties

Angle of Repose

$$\Theta = \tan^{-1} H/R$$

Θ=angle of repose

H=height of powder cone

R=radius of powder cone

Angle of Repose less than 30^0 shows the free flowing property of the material.

Loose bulk Density (LBD)
Df = M /Vp

Df = bulk density; M = weight of sample in grams
Vp = final volume of powder in cm^3

Tapped density (TD):
Do = M /Vp

Do = Tapped density; M = weight of sample in grams
Vp = final volume of powder after tapping in cm^3

Carr's consolidation index:

The Carr index is an indication of the compressibility of a powder. This is calculated by the formula

$$C = \frac{(q_b - q_t)}{q_b} \times 100$$

ρ_b is the bulk density; ρ_t is the tapped bulk density
A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability

Hausner's ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula

$$H = \rho_b / \rho_b$$

ρ_b is the bulk density; ρ_b is the tapped bulk density
Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Formulation of Oro dispersible tablets of Methadone

Composition of Methadone oro Dispersible Tablet by direct compression. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 8mm flat punch, B tooling. Each tablet contains 30 mg Methadone and other pharmaceutical ingredients. Total weight of tablet was found to be 120 mg.

Post Compression Parameters
Evaluation of uncoated tablets
Shape and colour

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by

$$F = \frac{[W(initial) - W(final)]}{W(initial)} \times 100$$

Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Drug Content estimation

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 258nm using UV Visible spectrophotometer (Lab India, UV-3200).

***In -vitro* dissolution studies**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800).

The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Methadone by measuring absorbance at 258 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8. Details:

Apparatus used: USP II Lab India DS 800
Dissolution Medium: Phosphate buffer PH 6.8 Dissolution Medium volume: 500ml
Temperature: 37^0C
Speed of paddle: 50rpm
Sampling Intervals: 2, 4, 6, 8, 10, 15, 20, 30, 45 & 60 min
Sample withdrawn: 5ml
Absorbance measured: 258 nm
Beers Range: 2-10µg/ml

Table 1. List of Materials Used

Name of the material	Source
Methadone	Natco LABS
Microcrystalline cellulose	Signet Chemical Corporation, Mumbai, India.
Sodium starch glycollate	SD fine chemicals, Mumbai, India.
Cross povidone	Merck Specialities Pvt Ltd, Mumbai, India.
Croos carmellose sodium	Merck Specialities Pvt Ltd, Mumbai, India.
Magnesium stearate	SD fine chemicalss, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India

Table 2. List of Equipment's used

Name of the Equipment	Manufacturer
Weighing Balance	Sartourious
Tablet Compression Machine (Multistation)	Cemach Limited, India.
Hardness tester	Sisco, Mumbai, India.
Vernier callipers	Mitutoyo, Japan.
Roche Friabilator	Labindia, Mumbai, India
DissolutionApparatus	Labindia, Mumbai, India
UV-Visible Spectrophotometer	Labindia, Mumbai, India
pH meter	Labindia, Mumbai, India
FT-IR Spectrophotometer	Per kin Elmer, United States of America.

Table 3. Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 4. Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Table 5. Composition of various tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Methadone (mg)	40	40	40	40	40	40	40	40	40
Sodium Starch Glycollate (mg)	12	24	36	-	-	-	-	-	-
Cross Povidone (mg)	-	-	-	12	24	36	-	-	-
Cross Carmellose Sodium (mg)	-	-	-	-	-	-	12	24	36
Magnesium Stearate(mg)	2	2	2	2	2	2	2	2	2
Talc(mg)	2	2	2	2	2	2	2	2	2
MCC(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	120	120	120	120	120	120	120	120	120

Table 6. Limits of Weight variation

Average Weight of Tablet(mg)	%deviation
130mg or less	10
> 130or <324	7.5
> 324	5

RESULTS AND DISCUSSION

Table 7. Concentration and absorbance obtained for calibration curve of Methadone In pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance* (at 258 nm)
1	2	0.107
2	4	0.215
3	6	0.299
4	8	0.402
5	10	0.507

Table 8. Pre-Compression Parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle of Repose(Ɵ)
F_1	0.45	0.55	18.18	1.22	27.91
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.50	0.58	13.79	1.16	29.34
F_4	0.46	0.55	16.36	1.19	26.71
F_5	0.50	0.58	13.79	1.16	29.34
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.50	0.58	13.79	1.16	29.34
F_8	0.41	0.50	18	1.21	26.78
F_9	0.41	0.50	18	1.21	26.78

Table 9. Post Compression Parameters

Formulation Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	120	2.5	3.59	20.33	0.43	97.23
F2	124	2.6	3.64	22.66	0.34	98.55
F3	119	2.5	3.59	30.33	0.49	98.16
F4	121	2.6	3.58	19.00	0.47	99.34
F5	122	2.3	3.59	30.33	0.49	98.16
F6	123	2.7	3.64	22.66	0.34	98.55
F7	122	2.5	3.59	30.33	0.49	98.16
F8	120	2.6	3.56	17.00	0.34	99.25
F9	122	2.5	3.56	17.00	0.34	99.25

Table 10. *In vitro* dissolution studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	25.43	30.8	45.72	24.39	31.76	48.32	28.43	39.55	110.4
2	39.65	36.72	66.16	31.67	34.54	82.96	35.25	76.34	110.3
3	48.62	56.16	101.16	49.35	41.96	98.74	48.94	96.23	
4	64.37	87.4		58.37	62.43		66.86	99.76	
5	76.49	98.5		74.35	89.14		78.13		
6	97.64			88.12	99.53		86.45		
7	97.16			94.61			99.45		
8				98.78					

Fig. 1. Standard graph of Methadone in pH 6.8 Phosphate buffer

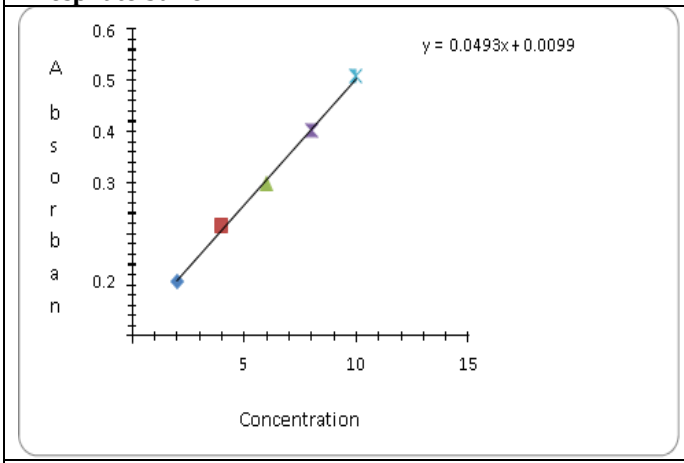


Fig. 2. Dissolution profile of formulations prepared with Sodium starch Glycollate as super disintegrate

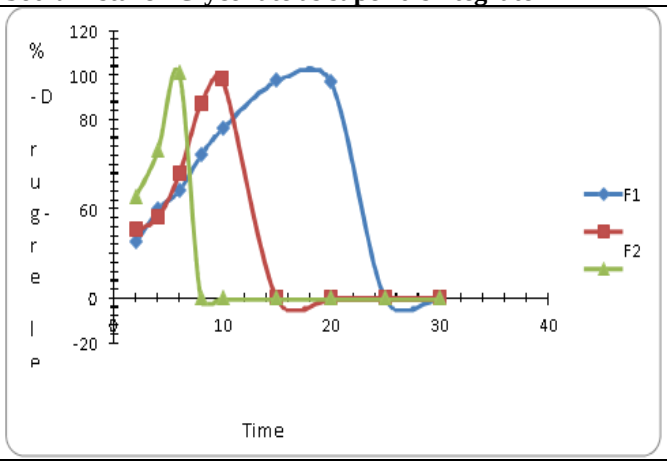


Fig. 3. Dissolution profile of formulations prepared with Cross Povidone as super disintegrate

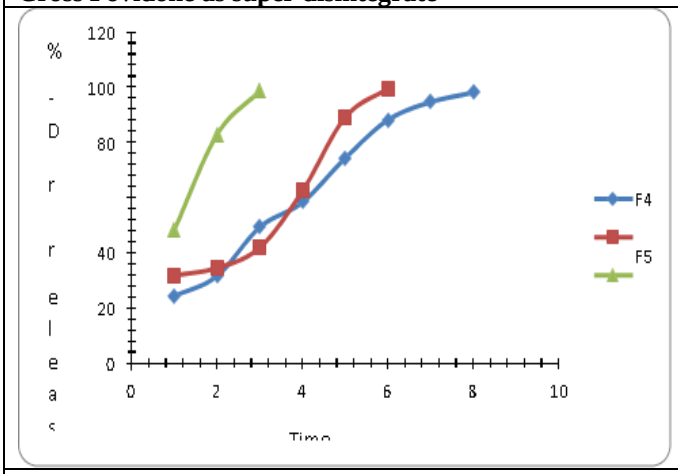


Fig. 4. Dissolution profile of formulations prepared with Cross carmellose sodium as super disintegrate

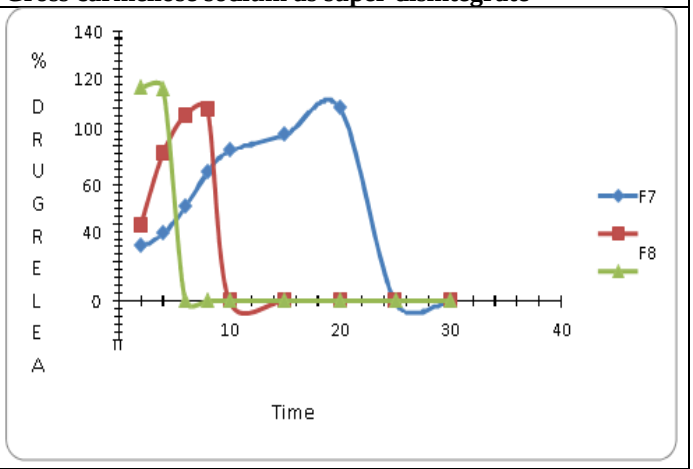
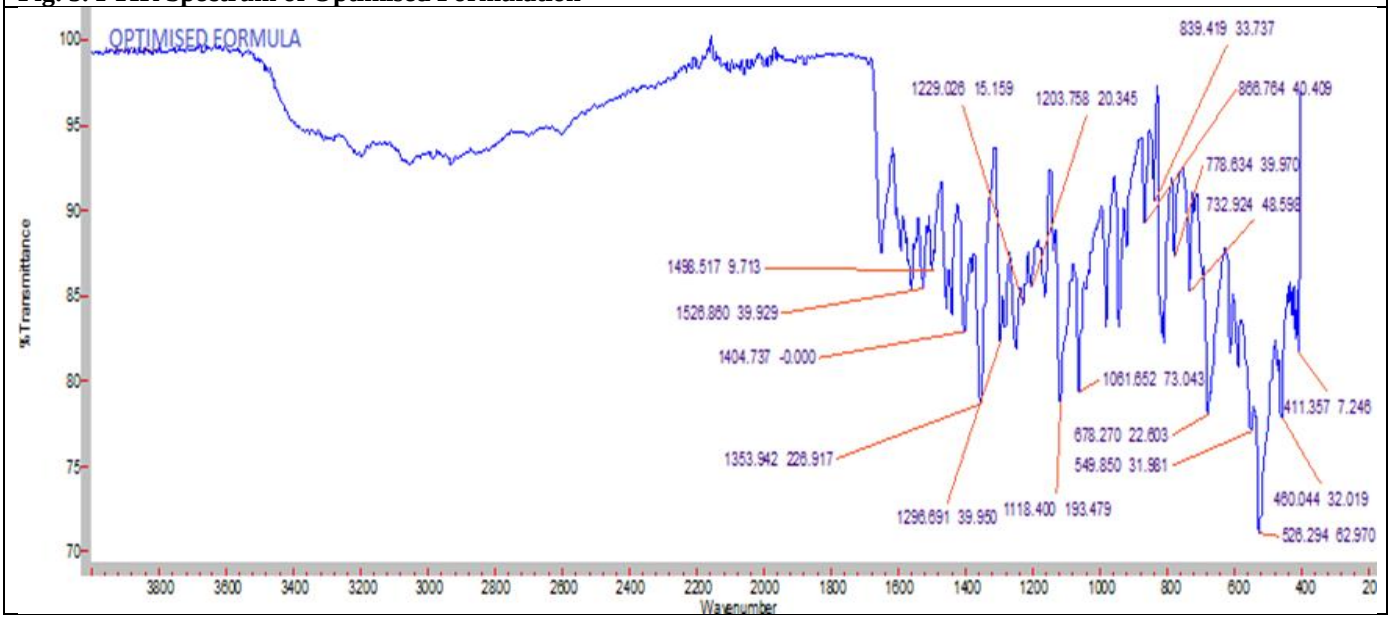


Fig. 5. FTIR Spectrum of Optimised Formulation



Standard Calibration curve of Methadone

It was found that the estimation of METHADONE by UV spectrophotometric method at λ_{max} 258nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2- 10µg/ml. The regression equation generated was y = 0.049x + 0.009, R^2 = 0.998.

Evaluation Parameters for Fast Dissolving Tablets of Methadone

Pre-compression parameters

The data's were shown in Table 7.2.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ration fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Assay

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 -99.2%.

***In vitro* Dissolution studies**

In vitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min.

From the tabular column (Table 10) it was evident that the formulations prepared with super disintegrate Cross carmellose sodium showed maximum % drug release in 2 min i.e.110.96% (F9 formulations and the concentration of super disintegrate was 36 mg). So the principle of super disintegrates was found to be useful to produce oro dispersible tablets. F9 formulation was considered as optimized formulation. The formulation followed zero order release mechanism. As the time increases the percentage drug release was increased.

CONCLUSION

In the present work, an attempt has been made to develop fast disintegrating tablets of Methadone. In the present work Sodium starch glycollate, Cross povidone and Cross carmellose sodium were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 98.78 % in 8 min hence it is considered as optimized formulation. The F4 formulation contains Cross povidone as super disintegrate in the concentration of 12 mg.

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