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Development and evaluation of Meloxicam solid dispersion loaded buccal patches

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ABSTRACT

Meloxicam, a non-steroidal anti-inflammatory drug is widely used in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. It is also indicated for the management of dental pain, Post-traumatic and post-operative pain, inflammation and swelling. Recently it is considered as a potential drug for prevention and treatment of colorectal polyps. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability and GI-Side effects after oral administration. The present work was aimed at overcoming these limitations of the drug. The first problem i.e. Poor solubility of meloxicam was overcome by solid dispersion technique and the same was than published in a reputed online journal. The present study was the continuation of the published work, in this study buccal patches were prepared using varying percentage of carbopol 934p, chitosan (mucoadhesive polymers) and 50% W/W of propylene glycol (Plasticizer) by solvent casting technique, using 3² factorial design. Prepared blank buccal patches were evaluated for various physical and mechanical parameters, patches which comply with reported results were selected for meloxicam and its solid dispersion incorporation. Meloxicam solid dispersion incorporated buccal patches were prepared and evaluated for drug content, in-vitro diffusion, in-vivo release of meloxicam in rabbits and stability study. All solid dispersion loaded patches showed increased in-vitro drug release (i.e. between 95% to 99.95%) over an extended period of 8hrs as compared to plain drug loaded buccal patch. Whereas plain drug loaded buccal patch showed only 31.22% in-vitro drug release in 8hrs. Meloxicam solid dispersion loaded buccal patch (MSP1) containing meloxicam solid dispersion (meloxicam 150mg, PVP250mg, PEG6000 175mg and mixture of lactose and MCC(4:1)4gm) equivalent to 7.5mg of meloxicam, 1.5% of carbopol 934p, 2% of chitosan and 50% of polymer weight of propylene glycol in each 1cm² of the patch showed highest in-vitro drug release i.e. 99.95% in 8hrs and it followed zero order release ($r=0.9961$, $a=8.3124$, $b=5.0668$). The r , a and b are correlation coefficient, slope and constant respectively for the best fit kinetic model. The in-vivo release of meloxicam from its solid dispersion loaded buccal patches was also studied using rabbit model. A good in-vitro in-vivo correlation was observed in MSP1 patch. All solid dispersion loaded buccal patches showed excellent stability under tested conditions. Finally it may be concluded that buccal patches were better for improvement of release of meloxicam and also to overcome the gastric side effects of drug.

Key words: Meloxicam; Solid dispersion; Buccal Patch; In-vitro release; In-vivo release

INTRODUCTION

Meloxicam is a nonsteroidal anti inflammatory drug (NSAID) belonging to the class of oxicams. In addition to its analgesic and antipyretic effect it is widely used in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis (Laurent, et.al, 2000) It is also indicated for the management of dental pain, Post-traumatic and post-operative pain, inflammation and swelling. Recently, meloxicam has been considered as a potential drug for the prevention and treatment of colorectal polyps and/or cancer (www.Drug Bank showing meloxicam.mht). And also it is one of the few NSAIDs approved for the use in animals (Source: www.manhattancats.com). Meloxicam is practically insoluble in water which leads to poor bioavailability. Anti-inflammatory

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agents are poorly soluble in gastric acid and, thus, remain in contact with the stomach wall for a longer period, consequently producing highly dangerous local concentrations. This leads to irritation of the stomach wall, stomach pains, ulceration, gastric perforation, and bleeding (Ellsworth et. al, 2004) The average risk of ulcers increases when the drug is used for prolonged periods. Geriatric patients who use NSAIDs exhibit a five-fold increase in the likelihood of serious gastrointestinal events. Thus, meloxicam is not suitable for the treatment of rheumatologic patients with gastric ulcer. Further the poor aqueous solubility and wettability of meloxicam leads to difficulty in preparing pharmaceutical dosage forms (Saleem et.al, 2010). Therefore the search continues for an effective NSAIDs with increased solubility and decreased gastrointestinal side effects. This could be achieved by formulating solid dispersions of meloxicam and loading the same into buccal patches. Buccal formulations containing solid dispersions of drug will have dual advantage (Hirlekar et.al, 2009) of increased solubility and avoidance of GI-side effects of poorly soluble drugs. Among various techniques of solubility enhancement, solid dispersion (SD), which was introduced in the early 1970s, is an effective method for increasing the dissolution rate of poorly soluble drugs, hence, improving their bioavailability. Chiou and Riegelman defined the term SD as 'a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method (Chiou et al, 1971) Buccal drug delivery has been considered as an interesting alternative to solve many of the problems associated with oral administration.

Meloxicam possesses appropriate physico-chemical properties for potential buccal delivery. It is highly potent, and the oral dose (7.5–15mg/d) of meloxicam is the lowest of any of the NSAIDs. It has a low molecular weight(354.1), low polarity and low daily therapeutic dose. Moreover, it has been reported that meloxicam formulations exhibit good local tissue tolerability (e.g. Ocular, rectal and dermal) (Patel et al, 2011) thus, they appear to be suitable for transmucosal (such as buccal) administration. Solid dispersion loaded systems such as tablets (Hirlekar et al, 2009), creams (Madhusudhan et al, 1999), gels (Saleem et al, 2010), suppositories (Gowthamarajan et al, 2002), suspensions (Ubaidulla et al, 2005), etc showed highest drug releasing property and increase in pharmacological activity of many poorly soluble drugs as compared to plain drug loaded systems. Therefore in this study an attempt was made to develop solid dispersion loaded buccal patches of meloxicam to provide ease of administration and eliminate GI side effects of meloxicam by releasing the drug completely and directly into the blood stream of the patient. The present study is a continuation of our work "enhancement of dissolution and anti-inflammatory effect of meloxicam using solid dispersions" which was published in International journal of applied pharmaceutics (Jafar et al, .2010).

MATERIALS AND METHODS

Meloxicam was obtained as a gift sample from Unichem laboratories Pvt Ltd Mumbai, Chitosan was obtained from Central Institute of Fisheries Technology, Cochin. Carbopol 934p,

mercury, and other excipients were purchased from S.D. Fine chem. Ltd, Mumbai. All other reagents and chemicals used were of analytical reagent grade. To investigate any possible interaction between the drug and the utilized polymer,

Fabrication of blank buccal patch

A 3² factorial design was used to prepare blank Buccal patches by solvent casting technique (Sahni.J,et.al.2008) employing mercury as a substrate. The casting solutions were prepared by dissolving appropriate polymers (Carbopol 934p and chitosan) and Propylene glycol in 5% acetic acid using magnetic stirrer for 20 min to get uniform dispersion. Propylene glycol added at a concentration of 50 % w/w of polymers. The solution was then transferred quantitatively to glass ring kept on the surface of mercury in petridish. Controlled solvent evaporation was achieved by placing an inverted funnel over the petridish. These were left undisturbed at room temperature for one day. The patches could be retrieved intact by slowly lifting from the mercury substrate and kept in the dessicator until used.

Evaluation of blank Buccal patches (Ponigrahi L, et. al.2005)(Khanna R,1997)

a. Physical appearance

All the buccal patches were visually inspected for colour, clarity, flexibility and surface texture.

b. Thickness uniformity

Discs of 1 cm² patch were subjected to measurement of thickness, using micrometer screw gage.

c. Folding endurance

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

d. Tensile strength and % Elongation

The tensile strength of the buccal patches was measured using tensile strength instrument (locally fabricated instrument). A small film strip (30 x 10 mm) was used. One end of the strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached to the other end to hold the weights. A small pointer was attached to the thread, which travels over scale on the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The weight required to break the film was noted as break force. The tensile strength was calculated by the formula,

$$\text{Tensile Strength} = \frac{\text{wt required to break film}}{a \times b \times (1 + \frac{1}{1})}$$

Where, a=thickness of film
 b=width of film
 l=length of film

The percent elongation was determined by noting the length just before the break point and substituting the formula

$$\% \text{ Elongation} = \frac{[\text{Final length} - \text{Initial length}] * 100}{\text{Initial length}}$$

e. Bioadhesive Strength

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance.

Instrument: The apparatus was locally assembled and was a modification of the apparatus applied by Parodi et al. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane.

Method: The fabricated balance described above was used for the bioadhesion studies. The bovine cheek pouch, excised and washed was fixed to the movable platform. The mucoadhesive patch was fixed of 3 cm², was fixed to the stainless steel lamina using 'fevi-quick' as adhesive. The exposed patch surface was moistened with 1 ml of isotonic phosphate buffer for 30 seconds for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into the contact with the mucosal surface. A preload of 20 gms was placed over the stainless steel lamina for 3 minutes as initial pressure. And then weights were slowly increased on the right pan, till the patch detaches from the mucosa give the bioadhesive strength of the mucoadhesive patch. The procedure is repeated for 3 times for each patch and mean value of the 3-trials was taken for each set of formulation. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before taking reading

f. Percent Swelling Index

The polymeric patches cut into 1 x 1 cm were weighed accurately and kept immersed in 50 ml of water. The patches were taken out carefully at 5, 10, 30 and 60 minutes intervals blotted with filter paper to remove the water present on their surface and weighed accurately, the percent swelling is calculated using formula:

$$\% \text{ swelling} = \frac{\text{Wet weight} - \text{dry weight}}{\text{Wet weight}} \times 100$$

g. Moisture Uptake

A modification of the ASTM method was used. Specimens were subjected to desiccation over sodium hydroxide at room temperature for 48 hours. This weight was recorded as the initial weight. These samples were then exposed to 74.9%, 52%

and 98%. Relative humidity (RH) using sodium chloride (NaCl), sodium bisulfate and potassium dichromate respectively in their saturated solution at room temperature. These specimens were weighed periodically until no further increase in weight was recorded. The moisture uptake was calculated at each RH as given below:

$$\frac{(\text{Final weight}) - (\text{Initial weight}) \times 100}{\text{Initial weight}}$$

This test is of great significance as variation in moisture content causes a significant variation in mechanical properties of the film especially when film comprises of a hygroscopic components, it is also important to assess such polymers, which are of humidity-dependent diffusiveness. The capacity of the film to take up water is an important intrinsic parameter of the polymeric system in consideration to the release of drug through mucous membrane.

h. Surface pH

The patches was allowed to swell then in contact with 0.5 ml of distilled water (pH 6.5±0.5) for one hour at room temperature and pH was noted down by bringing electrode in contact with the surface of the patch, allowing it equilibrate for 1 minute.

Fabrication of meloxicam solid dispersion loaded buccal patch

The buccal patches containing meloxicam solid dispersions were prepared by incorporating selected solid dispersions of meloxicam in selected polymer composite of carbopol 934p and chitosan. The polymers in selected % were dissolved 5% acetic acid solution. Then the solid dispersion equivalent to 45mg of meloxicam (Jafar et al, 2010). (i.e. 7.5mg/cm²) was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Propylene glycol in 50% w/w was used as plasticizer. Then the solution was poured on the Petri dish having mercury and dried at the room temperature. Controlled solvent evaporation was achieved by placing an inverted funnel over the petridish. These were left undisturbed at room temperature for one day. A patch of pure meloxicam with polymers and other additives was also prepared for comparison. The patches could be retrieved intact by slowly lifting from the mercury substrate and kept in the desiccator until further investigation.

Evaluation of meloxicam solid dispersion loaded Buccal patches

a. Drug Content Uniformity

1 cm² area of the patch was cut and each dissolved in sufficient quantity of methanol. The volume was made up to 10 ml. 1 ml was then withdrawn from this solution and diluted to 10 ml with suitable phosphate buffer. The absorbance was then measured at 362nm. From the absorbance and the dilution factor, the drug content in the film was calculated.

b. In Vitro Release Study

The release of meloxicam from the buccal patch was determined using Keshary-Chein diffusion cell (Patil et al, 2003).

The diffusion medium was phosphate buffer pH 6.8, maintained at 37°C. The parchment paper was soaked in phosphate buffer pH 6.8 for 1h and then air-dried. It was mounted between the donor and receptor compartment and film was placed on it. Both the compartments were clamped together. The phosphate buffer pH 6.8 was filled in the receptor compartment (11ml capacity) and stirred using magnetic stirrer. At different time intervals samples were withdrawn and replaced with an equal volume of buffer. The samples were analyzed spectrophotometrically after appropriate dilution at 362 nm.

c. Stability study

Stability study for meloxicam solid dispersion loaded buccal patches was carried out by storing the patches in a beaker lined with aluminium foil at different temperatures and relative humidity for a period of 3 months. The patches were visually examined for any physical change and drug content was estimated at the end of 3 months (www.ich.org).

d. In vivo drug release study in rabbits (Thimma Setty et al., 2008)

After the approval of institutional animal ethical committee the in-vivo absorption studies of meloxicam solid dispersion loaded buccal patch was conducted on rabbits. Three male rabbits (Siegel *et al.*, 1981) weighing 5.0, 5.5, and 6.0 kg of either sex were used for the release study of the meloxicam. The animals were fasted for overnight with *ad libitum* storing them in individual cages before the experiment was carried out. The rabbits were anesthetized with phenobarbital sodium IP (1 ml containing 200 mg) by intra peritoneal route. Patches of size 1 x 1 cm² were cut and fixed on a cellophane paper which acted as a backing layer so that the drug release was made unidirectional and threads tied to it, so that the patches were easily removed from the buccal cavity. After 30 min. of the anaesthetic injection, the patches were placed (separately) in the buccal cavity one at a time. After a gap of 2 min. further patches were attached. The patches were taken out at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8th hours. The process was repeated two more times to validate the result. The patches were dissolved in 10 ml of phosphate buffer, pH 6.8. The drug remained unabsorbed was analyzed at 362 nm.

RESULTS AND DISCUSSION

A 3² factorial design was used to formulate blank buccal patches. Carbopol 934p and chitosan were selected as bioadhesive polymers in the design of buccal patches because of their excellent bioadhesive properties. Propylene glycol has recently been reported to be a plasticizer, so it is selected as plasticizer in 50% W/W of polymer weight to impart flexibility and clarity to the patches. Buccal patches were prepared by solvent casting method and were evaluated for various parameters (Table-1). Surface PH of all blank patches was in the range of 5.83 to 6.8, this suggests patches are non-irritant to buccal mucosa. Percent Swelling index and Percent moisture uptake of blank patches was increased with increase in the concentration of polymers and also increase in the time of exposure and relative humidity respectively. (Figure-1 & 2).

Patches P6 to P9 were comply with the reported results (Amit khairnar. et al. 2009). Therefore these patches were selected for

Table 1: Factors and levels in the Design

Independent Variables	Levels		
	Low (-1)	Medium (0)	High (+1)
Carbopol 934p (X ₁) %	1	1.5	2
Chitosan (X ₂) %	1	1.5	2

Amount of Propyleneglycol(50% w/w of polymer weight) and Acetic acid(5%) was maintained constant in all the preparations.

Blank buccal patches and measured responses

Blank patch code	X ₁	X ₂	Surface texture	Folding Endurance	Elongation at Break	Mean Thickness (mm)	Tensile Strength (dynes / cm ² x 10 ⁷)	Bioadhesive Strength (g)
P ₁	-1	-1	V.S	126.33	11.23	0.86	2.41	140.66
P ₂	-1	0	V.S	196.00	19	0.89	3.12	150.65
P ₃	-1	+1	S	198.00	21.2	0.84	3.88	190.65
P ₄	0	-1	S	211.00	22.6	0.88	2.96	220.40
P ₅	0	0	S	225.60	23.2	0.87	3.86	230.50
P ₆	0	+1	S	269.66	28	0.89	3.12	260.58
P ₇	+1	-1	S	291.33	32.11	0.87	4.10	210.83
P ₈	+1	0	S	301.33	34.12	0.89	4.24	240.30
P ₉	+1	+1	S	300.00	33.91	0.88	3.89	280.13

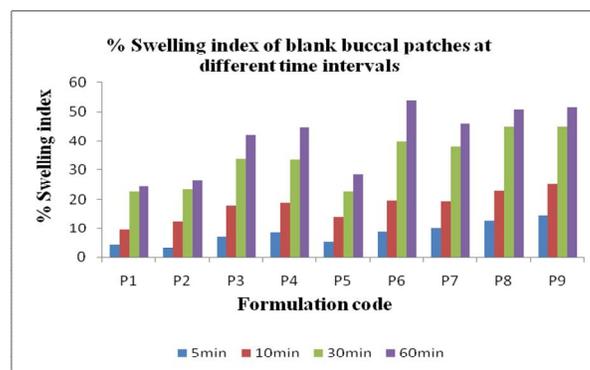


Fig: 1 Percent swelling index of blank buccal patches at different time interval.

meloxicam solid dispersion incorporation. A patch containing pure meloxicam was also prepared for comparison with solid dispersion incorporated buccal patches. An optimized meloxicam solid

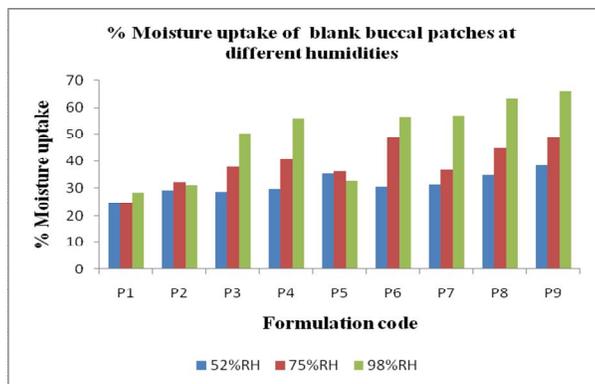


Fig: 2 Percent moisture uptake of blank buccal patches at different humidities.

dispersion formulation (Jafar et al, 2010) was incorporated to all P6 to P9 buccal patches (Table-3) and were evaluated for drug content, in-vitro drug release, stability study and in-vivo drug release in rabbits. The content of meloxicam in each patch was assayed by UV-spectroscopy. The meloxicam content of the prepared patches was found to be in the range of 98% - 100%, indicating the application of the preparation method for the preparation of buccal patches with high content uniformity.

Table 2: Composition of pure meloxicam/meloxicam solid dispersion loaded buccal patches

Sr.No	Ingredients	Buccal patch code				
		PMP	MSP1	MSP2	MSP3	MSP4
1	Pure meloxicam(mg)	45	-----	-----	-----	-----
2	Meloxicam Solid dispersion [*] (mg)	-----	45	45	45	45
3	Carbopol 934p(%)	1.5	1.5	2	2	2
4	Chitosan (%)	2	2	1	1	2
5	Propylene glycol(%)	50	50	50	50	50
6	Acetic acid(%)	5	5	5	5	5

Note: - ^{*} Indicates solid dispersion equivalent to 45 mg of meloxicam, PMP-Pure meloxicam loaded patch and MSP-Meloxicam solid dispersion loaded patch

The In-Vitro diffusion characteristics of different patches were compared with the pure drug. The solid dispersions of meloxicam loaded buccal patches showed almost 100% drug release over an extended period of 8 hrs when compared with pure meloxicam loaded buccal patch (Figure-3).

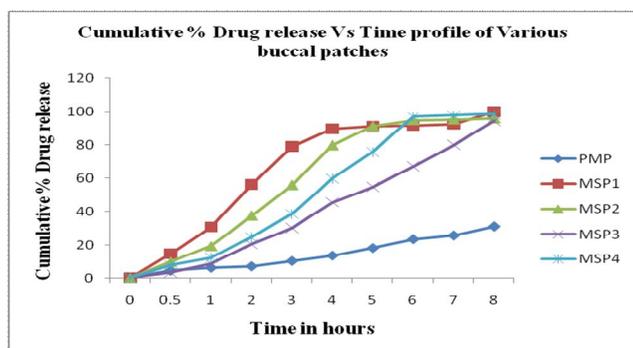


Fig : 3 Cumulative % release of meloxicam from buccal patches PMP, MSP1, MSP2, MSP3 and MSP4

Meloxicam solid dispersion loaded buccal patch (MSP1) containing meloxicam solid dispersion (meloxicam 150mg, PVP250mg, PEG6000 175mg and mixture of lactose and MCC 4gm) equivalent to 7.5mg of meloxicam, 1.5% of carbopol 934p, 2% of chitosan and 50% of polymer weight of propylene glycol in each 1cm² of the patch prepared by solvent casting method showed highest drug release i.e. 99.95% in 8hrs. The release mechanism of meloxicam from various patches was studied. The data was treated to study the best linear fit for the following equations (Costa et al, 2001)

- 1) Zero order ----- % R=Kt
- 2) First order ----- log % unreleased = Kt/2.303
- 3) Matrix (Higuchi matrix) ----- % R=Kt^{0.5}
- 4) Peppas – Korsmeyer equation -----

$$\left[\frac{\text{Amount of drug released at time 't'}}{\text{Amount of drug release at '}\infty\text{'}} = Kt^n \right]$$

- 5) Hixson – Crowell equation ----- (% unreleased)^{1/3}=Kt where 'n' is the diffusion coefficient which is indicative of transport mechanism.

The best fit model for MSP2, MSP3 followed zero order release. Whereas MSP4 showed super case-II transport. The mechanism of drug release for highest drug releasing patch MSP1 was also zero order release (r=0.9961, a=8.3124, b=5.0668). The r, a and b are correlation coefficient, slope and constant respectively for the best fit kinetic model. Meloxicam solid dispersion loaded buccal patches were tested for stability with respect to physical texture, assay and In-vitro drug release by placing them in a glass beaker lined with aluminium foil at accelerated (40^o c / 75% RH) and controlled room temperature (25^o c / 60% RH) conditions for 3 months. The results are appended in Table-4. The results indicated the formulations were stable under the tested conditions of storage.

The concept of in-vitro, in-vivo correlation studies were used in pharmaceutical research work, because a simple in-vitro release study on a drug product will be insufficient to predict its therapeutic efficiency. So correlation between in-vitro release behaviour of a drug and its in-vivo absorption in rabbits must be demonstrated experimentally to reproduce therapeutic response. The in-vivo release data of meloxicam from its solid dispersion loaded buccal patch (MSP1) was almost similar to that of in-vitro drug release data of the same patch, this data clearly indicates good in-vitro in-vivo correlation of MSP1 patch. The in vitro diffusion and in-vivo release of meloxicam solid dispersion incorporated buccal patches was greatly improved when compared with those of pure meloxicam incorporated patches. From overall formulations MSP1 was found to be the best buccal patch. From the above results, it may be concluded that buccal patches were better for improvement of release of meloxicam and also to overcome the gastric side effects of drug.

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Table 3: Evaluation of storage stability of the meloxicam solid dispersion loaded buccal patches

Formulation code	Physical texture			% Drug content			Cumulative% Drug release (8 th hr)		
	Initial	25 ^o c	40 ^o c	Initial	25 ^o c	40 ^o c	Initial	25 ^o c	40 ^o c
		60% RH 3M	75% RH 3M		60% RH 3M	75% RH 3M		60% RH 3M	75% RH 3M
MSP ₁	smooth	smooth	smooth	98	99	98	99.95	99.63	99.15
MSP ₂	smooth	smooth	smooth	99	98	98	95.94	95	94.97
MSP ₃	Smooth	Smooth	Smooth	98	98	97	94.29	94.19	94.10
MSP ₄	Smooth	Smooth	Smooth	98	97	98	98.62	98.89	98.13

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