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Original article

HPMC Based Extended Release Matrix Tablet of Gabapentin by Direct Compression Method

Manish R. BHISE*, Sumedh P. MOHOD, Mahesh B. NARKHEDE, Sandip B. SAPKAL*

IBSS College of Pharmacy, Department of Pharmaceutics, Malkapur, Dist. Buldana 443101 (MS), INDIA

The purpose of this work was to develop extended release (ER) matrix tablets of gabapentin, an anticonvulsant drug. The tablets were prepared by direct compression method along with hydrophilic matrix materials like HPMC K4M, HPMC K 15M and HPMC K 100M. The blends were evaluated for bulk density, angle of repose and compressibility index. The tablets subjected to thickness, diameter, weight variation test, drug content, hardness, friability, and in vitro release studies in 0.1N HCl solution for the initial 2h, followed by pH 6.8 phosphate buffer solutions up to 12 hours. The drug release study revealed that matrix tablets containing HPMC K 15M and HPMC K 100M polymer exhibited more extended release than the tablets containing other polymers. Formulation F7 showed desired drug release up to 12 h. For the optimized formulation, kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport. Fitting the in vitro drug released data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release in optimized formulation F7.

Key words: Gabapentin, Extended release (ER), Direct compression, Micromeritics, Dissolution kinetics

Gabapentin'in Doğrudan Basım Yöntemiyle Hazırlanmış HPMC Bazlı Uzatılmış Salım Yapan Matrix Tableti

Bu çalışmanın amacı, bir antikonvülsan olan gabapentinin uzatılmış salım yapan matris tabletlerini geliştirmekti. Tabletler, HPMC K4M, HPMC K 15M, HPMC K 100M gibi hidrofilik matris materyalleri ile doğrudan basım yöntemi ile hazırlandı. KarışımLar, küme dansitesi, yığın açısı ve basılabilirlik indeksi açısından değerlendirildi. Tabletler, kalınlık, çap, ağırlık varyasyon testi, etken madde içeriği, sertlik, friabilite ve ilk 2 saatte 0.1 N HCl çözeltisi ve takip eden 12 saat boyunca da pH 6.8 fosfat tamponunda *in vitro* çözünme hızı çalışmalarına tabi tutuldu. Etken madde salım çalışmaları, HPMC K 15M ve HPMC K 100M polimerlerini içeren matris tabletlerde diğer polimerleri içeren tabletlerden daha uzun süreli salım olduğunu ortaya çıkardı. F7 formülasyonu 12 saate kadar süren istenilen salımı gösterdi. Optimize formülasyon için, *in vitro* çözünme profillerinin kinetik modellemesine göre etken madde salım mekanizmasının difüzyon kontrollü veya Fick transporttan anomolus tip ya da non-Fick transporta değiştiği bulundu. *In vitro* etken madde salımı verileri Korsmeyer eşitliğine uygulandığında optimize F7 formülasyonunda etken madde salım mekanizmasının difüzyonla birlikte erozyon olabileceği gösterildi.

Anahtar Kelimeler: Gabapentin, Uzatılmış salım, Doğrudan basım, Mikromeritik, Çözünme kinetikleri

***Correspondence:** E-mail: manishbhise.patil@gmail.com, Sandipsapkal1985@gmail.com

INTRODUCTION

Historically, the oral route is the most frequently prescribed for drug administration. Tablets are considered to be the most desirable dosage form for drug delivery, since it is preferred by patients and industry. Conventional dosage forms containing drugs with a short elimination half-life must be administrated several times a day to maintain an effective plasma level of the drug, which represents a major drawback in terms of patient compliance. As such, to improve the therapeutic efficacy of oral drug administration, with effective plasma levels for prolonged periods, Pharmaceutical R&D has focused on the development of oral drug delivery systems (sustained, extended, slow action, prolonged, controlled, delayed, pulsed, etc.) (1–7). Oral-controlled release technologies have been developed in an attempt to improve patient's quality of life (QOL) by reducing the inconvenience caused by the frequent dosing of conventional tablets. The hydrophilic gel-forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping (8-10). Extended release formulation is an important program for new drug research and development to meet several unmet clinical needs. There are several reasons for attractiveness of these dosage forms viz. provides increase bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. As these will release the drug slowly into the GIT and maintain a constant drug concentration in the plasma for a longer period of time (11).

Most commercially available extended release dosage forms employ hydroxypropylmethylcellulose (HPMC) as matrix-forming agents. The HPMC presents a low cost and easy to manufacture, offers little risk of release of the total drug dose (dose dumping effect), provides appropriate release kinetics, and has been extensively studied. Furthermore, pH-independent drug release is preferable for oral extended release formulations, so as not to be affected by intra- and inter-subject variations of both gastric pH and GI transit time. HPMC is a pH-independent material and the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant (12). However, the mechanism that controls the release of these systems is the gelling of HPMC, which is not always ideal for controlling the release of highly soluble drugs. Often, large amounts of HPMC are required. Another problem is that HPMC is poorly compactable and poor flow characteristics making it unsuitable for direct tabletting, and wet granulation can generate rigid particles (13). Some studies revealed that there is insufficient drug absorption from controlled release products in *in vivo* studies because of the suppression of drug release due to the environment of the colon (small volume of GI fluid and viscous colonic content) in the later stage (14–16). So, incorporation water-soluble excipients such as polyethylene glycol, lactose and surfactants into the gel-forming matrix can improve the phenomenon of insufficient drug release and/or absorption because these excipients can stimulate the water penetration into the inner parts of the matrix, thus resulting in drug release from matrix. Lactose is a soluble excipient and has been widely used in tablet dosage form (17–20). Microcrystalline cellulose (MCC) is often regarded as one of the best excipients for direct compression (21). Incorporated MCC into the formulation was shown to increase dissolution rates and compressibility of tablets made by high shear granulation (22).

In this study for once-daily gabapentin extended-release dosage forms, HPMC was used as a retardant, and the MCC as well as lactose were used to modify the drug release and ensure that most of drug is released in a period time comparable to the gastrointestinal residence time (23).

Gabapentin is an anticonvulsant drug. Gabapentin is slowly and partially absorbed from the gut. It is taken orally in the form of tablets of 300 mg, 400 mg, 600 mg and 800 mg. A unique feature of gabapentin oral absorption is that its bioavailability is not proportional to dose (such that as dose increases, bioavailability decreases). For example, 400 mg dose is about 25 %

less bioavailable than 100 mg dose. The mechanism by which gabapentin exerts its anticonvulsant action is unknown. Gabapentin is structurally related to the neurotransmitter GABA (gammaaminobutyric acid),but its mechanism of action is different from that of several other drugs that interact with GABA synaptic receptors, including valproate, barbiturates, benzodiazepines, GABA agonists, GABA uptake inhibitor and GABA prodrugs (24).

MATERIALS AND METHODS

Gabapentin was obtained as a gift sample from Torrent Pharmaceuticals, Ltd Ahmadabad. HPMC (K4M, K15M and K100M) were obtained as a gift from ISP, Hyderabad. Sodium hydroxide and potassium dihydrogen orthophosphate was obtained as a gift sample from Merck Specialties Pvt. Ltd. Microcrystalline cellulose was obtained as a gift sample from Dr. Reddy's Lab, Hyderabad. Lactose was obtained as a gift sample from S.D Fine Chemicals, Mumbai.

Formulation of gabapentin tablets

ER Matrix tablets were prepared by direct compression method. Gabapentin was mixed with the required quantities of polymers blend (HPMC K4M, K15 and K100) diluents lactose, microcrystalline cellulose and binders PVP K40 were used for the preparation of matrix tablets. The powders were blended thoroughly using a pestle and mortar. The powder blend was then lubricated with magnesium stearate and mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine (Cad mach, Ahmadabad, India). Tablets (500 mg) were compressed using a 12 mm Round-faced punch with the resistance to crushing between 150 and 200 N. Table 1 gives the details of the various formulations.

Physical evaluation of powder

The physical properties of granules were determined as follows

Bulk density

LBD (loose bulk density) and TBD (tapped bulk density) were determined by 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was placed into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The reading of tapping was continued until no further change in volume was noted (24).

LBD and TBD were calculated

LBD =Weight of the powder/volume of the packing

(equation 1)

TBD =Weight of the powder/tapping volume of the packing

(equation 2)

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index (25).

Carr's index (%) = {(TBD-LBD) ×100}/TBD

(equation 3)

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (26).

Angle of repose $\theta = \tan^{-1} h/r$

(equation 4)

Where, '*h*' is height of the powder cone, and '*r*' is the radius of the powder cone.

Evaluation of matrix tablets (31)

Tablet description

General appearance of tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or an odor, taste, surface texture, physical flaws and Consistency and legibility of any identify markings (27).

Thickness

The thicknesses of the tablets were determined by using a calibrated vernier caliper. 10 tablets from each batch were used, and average

Table 1. Quantity of raw materials per tablet (mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7
Gabapentin	300	300	300	300	300	300	300
HPMC K4M	110	---	---	80	90	---	---
HPMC K15M	---	120	---	---	---	40	50
HPMC K100M	---	---	130	---	---	50	50
Lactose	---	---	---	30	40	20	20
MCC	33	23	13	33	13	33	23
PVP K40	45	45	45	45	45	45	45
Mg Stearate	7	7	7	7	7	7	7
Talc	5	5	5	5	5	5	5
TOTAL	500	500	500	500	500	500	500

values were calculated (28).

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. 20 tablets were randomLy picked from each batch and hardness of the tablets was determined (29).

Friability test

The friability of tablets was determined using Roche friabilator. It is expressed in Percentage (%).After weighing, 10 tablets from each batch were rotated for 100 revolutions and then re-weighed to test for the percentage loss of weight. Percentage friability of tablets less than 1% is considered acceptable (30).

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method (31).

Drug content uniformity test

To determine the drug content, 10 tablets was crushed and powder containing 300 mg of Gabapentin was dissolved in 100 mL of phosphate buffer. The solution was passed through a whatmann (No. 1) filter, from this 1 mL of solution was withdrawn and volume made up to 100 mL using buffer and analyzed spectrophotometrically at 210 nm after sufficient with distilled water and concentration of the drug in the sample was calculated (32).

Swelling studies

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation (33).

$$\mathbf{Wu} = \frac{\mathbf{(Wt - Wo)x100}}{\mathbf{Wo}}$$

(equation 5)

Here, W_t as weight of the dosage at time t and W_o as initial weight of dosage form.

In vitro drug release study

Drug release from the matrix tablets were investigated using USP 22 I dissolution apparatus (Electro lab, India) equipped with eight paddle at the stirring speed of 100 rpm using 900mL 0.1N HCl solution for the initial 2h, followed by pH 6.8 phosphate buffer solution up to 12 hours. The dissolution medium was maintained at 37±0.5°C. At the interval of 1 hour 5 mL of the sample was withdrawn from the dissolution media and the same amount was replaced with fresh buffer to maintain the sink conditions. The concentration of gabapentin was determined using a UV spectrophotometer at the λ_{max} of 210 nm (33, 34).

Drug release kinetics

The release data obtained were treated according to zero-order ($R=K_1t$) first-order ($R=K_2t$), Higuchi ($R=K3\sqrt{t}$), korsmeyer-peppas ($\log R= K_4 + n \log t$) equation. Hixon-crowell equations

((UR) $^{1/3}$=K_5t) to find the equation with the best fit. Where R & UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, k_4 & k_5 are the rate constants of zero-order, first-order, Higuchi matrix, Korsmeyer-Peppas, and Hixon-crowell model, respectively (35-37).

RESULTS AND DISCUSSION

In this study, tablets of all the proposed formulations (F1 to F7) were prepared from different grades of HPMC (K4M, K15M and K100M) by direct compression method (Table 1). These polymers were utilized alone (F1 to F5) or in combination (F6 to F7) to evaluate their ease of manufacture and extent of release retardant effects. Formulations (F1 to F2) contained HPMC K4M and K15M exhibited physical problems were lowering hardness, surface cracking, and breakdown into pieces during dissolution. Similarly, formulations (F3) prepared utilizing HPMC K100M showed very high hardness, capping, and difficulty in sieving and individual variation in release. Formulations (F4 to F5) prepared from K4M and lactose to modify the drug release. However, tablets (F6 to F7) were prepared from combination of HPMC K15M, HPMC K100M and lactose which was free from all the physical problems appeared in earlier formulations (26, 38- 40).

The blends of different proposed formulations (F1 to F7) were evaluated for LBD, TBD, compressibility index and angle of repose (Table 2). The results of LBD and TBD ranged from 0.255 ± 0.001 to 0.414 ± 0.002 and 0.274 ± 0.003 to 0.453 ± 0.001, respectively. The results of compressibility index (%) ranged from 5.86 ± 0.04 to 10.0 ± 0.04. Generally, compressibility index values up to 15% result in good to excellent flow properties. The results of angle of repose ranged from 31.1 to 36.2. The results of angle of repose (< 30) properties indicate almost well.

The thicknesses of tablets in all formulations were ranged from 5.2 ± 0.06 mm to 5.3 ± 0.05 mm. The weight variation of tablets in all formulations were ranged from 948±0.15% to 952.61 ± 0.31%.The hardness of all the formulations F1-F7 was found to be 6.4 ± 0.2 (kg/cm) to 7.4 ± 0.5 (kg/cm2). The friability of all the F1-F7 formulations was found to be 0.63% to 0.76 % respectively. Drug content of all the formulations were ranged from 99.11 ± 0.14 % to 99.61 ± 0.03 %. All the values are given in (Table 3). The % swelling index of all the formulations is given in (Table 4).

In vitro drug release study of formulations

The dissolution studies were carried out by USP 22 apparatus I, paddle method in all batches. The results of dissolution studies indicated that formulations F1, F2, F3 releases 99.47 %, 98.64 %, 97.69 % of drug at the end of 7, 9, 10 hours respectively. Formulations F4, F6 releases 102.43 % and 101.84 %, of drug in 11 and 10 hrs respectively, and finally formulations F5, F7 releases and 97.69 % and 98.81 % of drugs in 12 hrs, respectively.

Drug release kinetics

Different models like Zero order, first order, Higuchi's, and Peppas plots were drawn for formulation F1 to F7. The regression coefficient (R^2) value for Zero order, First order, Higuchi's, Hixon-Crowell, and Peppas plots (Table 5) for formulation F7 was found to be 0.9069, 0.8794, 0.9878, 0.9803 respectively. To confirm the diffusion mechanism, the data was also analyzed with Korsmeyer-Peppas model showing a good range of linearity, which appears to indicate a coupling of diffusion and erosion mechanisms so called anomalous diffusion. Hence, diffusion coupled with erosion might be the mechanism for the drug release from HPMC based matrix tablet.

CONCLUSION

The synthetic hydrophilic matrix of HPMC alone could not extend the release of the gabapentin effectively for 12 h. In this study for once-daily gabapentin extended-release dosage forms, HPMC was used as a retardant, and the MCC as well as lactose were used to modify the drug release. Results of the present study demonstrated that combination HPMC K15 and K100M polymer could be successively employed for formulating extended release matrix tablets, diffusion coupled with erosion might be the mechanism for the drug release from matrix tablets which can be expected to reduce the frequency of administration and decrease

the dose-dependent side effects associated with repeated administration of conventional gabapentin tablet. It was found that both MCC and lactose can increase the release rate, and the

Table 2. Physical Properties of all formulations

Formulation	Angle of repose (Θ)	Bulk density (gm/mL)	Tapped density(gm/mL)	Compressibility Index (%)
F1	32.1	0.294±0.002	0.318±0.002	7.54 ± 0.02
F2	33.4	0.273± 0.001	0.302±0.001	6.74 ± 0.04
F3	36.2	0.304± 0.002	0.340±0.001	10.0 ± 0.02
F4	34.2	0.272± 0.001	0.290±0.003	5.86 ± 0.04
F5	32.7	0.414± 0.002	0.453±0.001	10.0 ± 0.04
F6	33.0	0.304± 0.002	0.326±0.004	6.42 ± 0.02
F7	31.1	0.255± 0.001	0.274±0.003	6.56 ± 0.01

Table 3. Physicochemical characteristics of prepared tablets

Formulation	Shape & Color	Thickness (mm) Mean± S.D	Diameter (mm) Mean± S.D	Weight Variation (mg) Mean±S.D	Hardness (kg/cm^2) Mean± S.D	Friability	Drug content
F1	Circular, White	3.87±0.11	12.05±0.030	499±5	5.5± 0.24	0.191	98.96±0.22
F2	Circular, White	3.90±0.07	12.00±0.043	498±5	5.6± 0.12	0.290	97.86±0.34
F3	Circular, White	3.89±0.09	12.04±0.020	501±5	6.1± 0.21	0.146	98.75±0.32
F4	Circular, White	4.01±0.12	12.02±0.054	499±5	5.8± 0.14	0.149	99.72±0.30
F5	Circular, White	3.98±0.18	12.07±0.022	497±5	5.9± 0.12	0.201	98.90±0.22
F6	Circular, White	3.93±0.10	12.04±0.059	502±5	5.8± 0.21	0.193	98.82±0.34
F7	Circular, white	3.81± 0.02	12.21 ± .009	500±5	5.9± 0.14	0.46	99.06±0.29

Table 4. Percentage swelling index of formulated tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	15.5	17.5	27.5	14.3	12.5	31.21	39.2
2	22.34	24.34	42.59	20.09	18.3	41.4	61.34
3	27.14	30.4	55.16	28.34	21.78	53.8	77.31
4	31.98	41.34	53.20	35.67	23.34	65.5	75.03
5	36.45	48.14	49.20	33.21	27.34	53.3	65.04
6	38.67	36.87	45.01	29.04	29.59	57.43	59.00
7	33.4	45.84	33.01	27.23	25.23	53.61	54.02
8	28.3	38.56	25.03	26.34	19.9	48.43	48.57
9	25.9	32.4	19.14	24.8	16.45	39.23	42.21
10	19.34	26.5	15.09	20.35	13.6	36.45	33.8
11	14.34	22.8	14.06	23.8	10.34	32.46	24.27
12	11.1	20.5	12.08	27.4	8.45	27.91	19.2

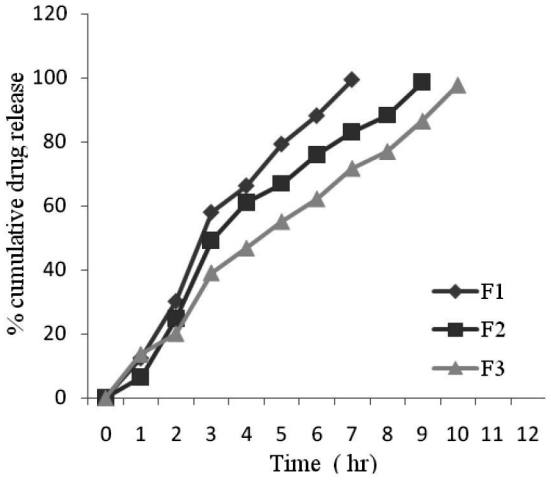

Figure 1. *In vitro* Drug release of formulation F1, F2, F3

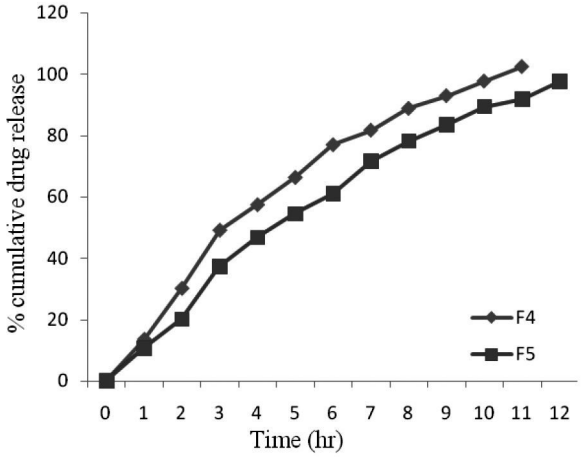

Figure 2. *In vitro* Drug release of formulation F4, F5

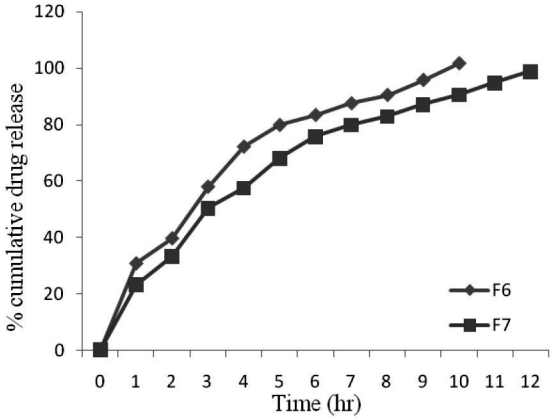

Figure 3. *In vitro* drug release from formulations F6, and F7

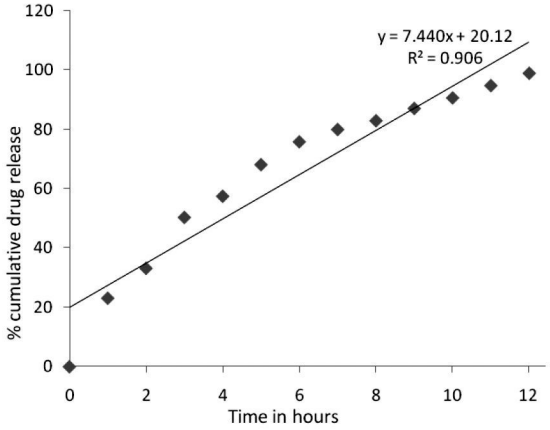

Figure 4. Drug release Kinetics of gabapentin from tablets of F7 batch.

Table 5. Kinetics of drug release of tablets label claimed 300 mg (Model fitting for formulation F7)

Time (hr)	$\sqrt{Time}$	Log time	Cumulative % drug release	Log cumulative % drug release	% of drug remained	Log % of drug remained	$M_t^{1/3}$-$M^{1/3}$
0	0	0	0	0	0	0	0
1	1	0	23.09211	1.3634	76.91	1.88	4.2526
2	1.41	0.3010	33.15789	1.5205	66.85	1.82	4.0585
3	1.73	0.4771	50.32895	1.7018	49.68	1.69	3.6761
4	2.0	0.6020	57.43421	1.7591	42.57	1.62	3.4916
5	2.23	0.6989	68.09211	1.8330	31.91	1.50	3.1718
6	2.44	0.7781	75.78947	1.87960	24.22	1.38	2.8932
7	2.64	0.8450	79.93421	1.9027	20.07	1.30	2.7175
8	2.82	0.9030	82.89474	1.9185	17.11	1.23	2.5768
9	3.0	0.9542	87.03947	1.9397	12.97	1.11	2.3495
10	3.16	1.00	90.59211	1.9570	9.41	0.97	2.1112
11	3.32	1.0413	94.73684	1.9765	5.27	0.72	1.7402
12	3.46	1.0791	98.88158	1.9951	1.12	0.049	1.0384

enhancement effect of lactose was higher than MCC.

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