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Development and evaluation of multiple unit particulate system (MUPS) of topiramate for taste masking

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ABSTRACT: Multiple unit particulate system (MUPS) is a more recent, challenging, effective and attractive option for the pharmaceutical industries that gives an efficient way to deliver the drug in modified pattern. MUPS are the most preferred dosage forms considering their ease of administration and consistency in manufacturing. Topiramate, indicated for schizophrenia, has a very bitter taste. The aim of this study was to develop a MUPS dosage form for taste masking of topiramate. Inert sugar spheres were coated with topiramate by fluid bed technique using povidone as binder. The drug loaded pellets were taste masked with cellulose acetate as taste masking agent. In the taste masking coating also, povidone was used as a binder and pore former. Developed taste masked MUPS were evaluated for polymorphic changes, drug content and dissolution in various media. Drug content of all batches of MUPS were within the range of 95-105%. Dissolution profile of the taste masked topiramate MUPS in 0.1N HCl, acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) was found to be satisfactory.

KEYWORDS: Taste masking; MUPS; Topiramate; Fluid Bed processor.

1. INTRODUCTION

Oral solid dosage forms are the most preferred drug delivery systems due to their ease of administration, easy handling, and cost effectiveness [1]. The oral route provides maximum surface area for drug absorption [2]. Tablets and capsules are the most preferred and well-established pharmaceutical products. Oral drug delivery systems can be broadly classified into immediate release and modified release dosage forms [3]. Immediate release oral dosage forms do not contain any specific polymers to modulate drug release profile and thus allow rapid release of the drug after oral administration [4].

Polymer-coated multiple-unit particulate systems (MUPS) are gaining significant interest of formulation scientist for oral drug delivery applications [5]. MUPS offer advantages, such as higher processing speed, lower cost of processing, rapid processing, and ease of administration. The MUPS system has various regulatory advantages, such as the extension of patent life and line extension of the product [6-14]. However, limited products are available in the market which contains MUPS. Therefore, this is the most flourishing field that needs to focus more on the development of such formulations [7].

Topiramate is only weakly effective in blocking chronic seizures induced by GABA receptor antagonist, pentylenetetrazole. It is chemically designated as 2,3:4,5-Di-O-Isopropylidene-(beta)-D-fructopyranose sulfamate. Absorption of topiramate is rapid, with peak plasma concentrations occurring in 2 hours. Topiramate is not extensively metabolized and is primarily eliminated unchanged in urine [8].

The purpose of this study was to mask the taste of topiramate and to improve the patient compliance. To achieve these goals, the taste masked MUPS was formulated using polyvinyl pyrrolidone K-30 and cellulose acetate [9- 12]. Preliminary trials were carried out to select the inert carrier and then binder and taste masking polymer. The formulation development of MUPS was divided into two phases: (i) drug layering on the inert carrier i.e., sugar spheres and (ii) taste masking. Dissolution of taste masked pellets was carried out in different biorelevant media to simulate biological conditions.

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2. RESULTS AND DISCUSSION

The X-ray powder diffraction patterns of topiramate and the final formulations are given in Figure 1. The PXRD pattern indicates that there was no change in the polymorphic form of topiramate during the MUPS preparation as well as after 3 and 6 months of stability studies at 40° ± 2°C / 75 ± 5% RH. The crystalline form of the drug was retained throughout the study.

The saturation of solubility of topiramate is given in Table 1. The drug exhibited good solubility in water and across the complete physiological pH range (pH 1.2 to 6.8). From the solubility studies, it is evident that the drug is freely soluble. Keeping in view of the better discriminatory power, 0.1N HCl was selected as dissolution medium.

Table 1. Saturation solubility of topiramate at different pH.

Solvent	Approximate pH	Solubility (mg/mL)	Dose/Solubility Ratio
Purified Water	5.86	12.05	2.07
0.1 N HCl	1.2	11.12	2.25
0.01 N HCl	2.0	11.22	2.23
Acetate Buffer	4.5	12.39	2.02
Phosphate Buffer	6.8	10.77	2.32

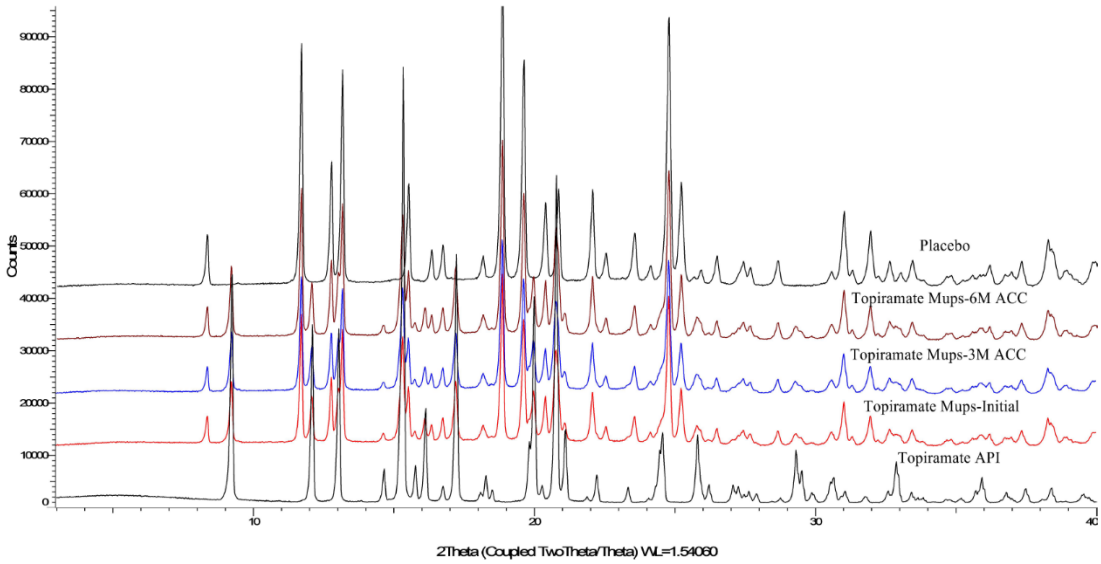

Figure 1. PXRD of topiramate and its MUPS formulations.

In the drug excipient compatibility study, the FTIR peaks of samples stored at 40°C/75% RH in open vials for 1 month are shown in Figure 2 and the DSC thermograms are given in Figure 3. In the infrared spectra of formulation, the peaks of topiramate were not changed, which is shown by the match in the spectra. This indicates the absence of any interactions between drug with excipients.

DSC thermogram of drug showed an endothermic peak at 124°C corresponding to its reported melting point. On the other side, shift in the thermogram of drug was observed and peak was showed at 125°C difference in the melting points of pure drug and formulation was an indication of the increased solubility of the drug.

The impact of particle size distribution is given in Figure 4. The studied range of drug particle sizes did not show any significant impact on product dissolution. This might be due to the good aqueous solubility of the drug.

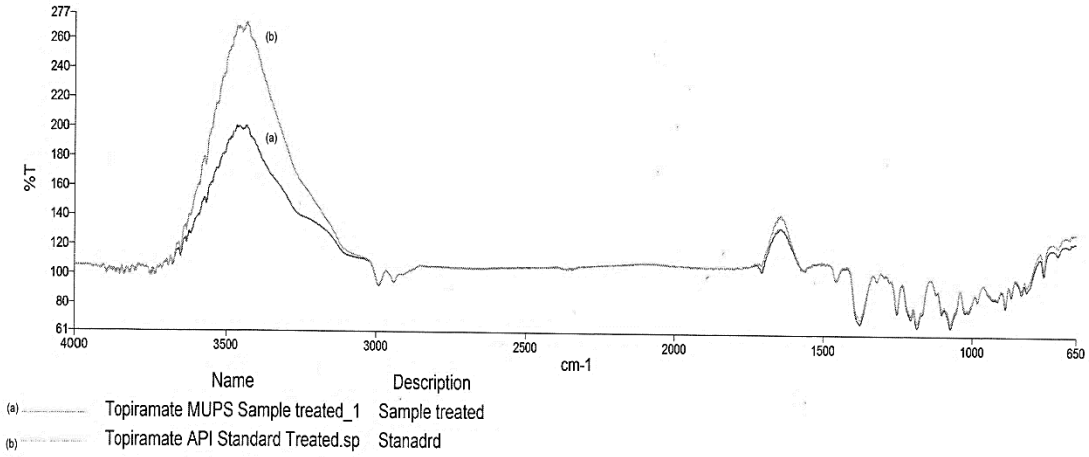

Figure 2. FTIR spectra of topiramate (a) and the optimized MUPS formulation (b).

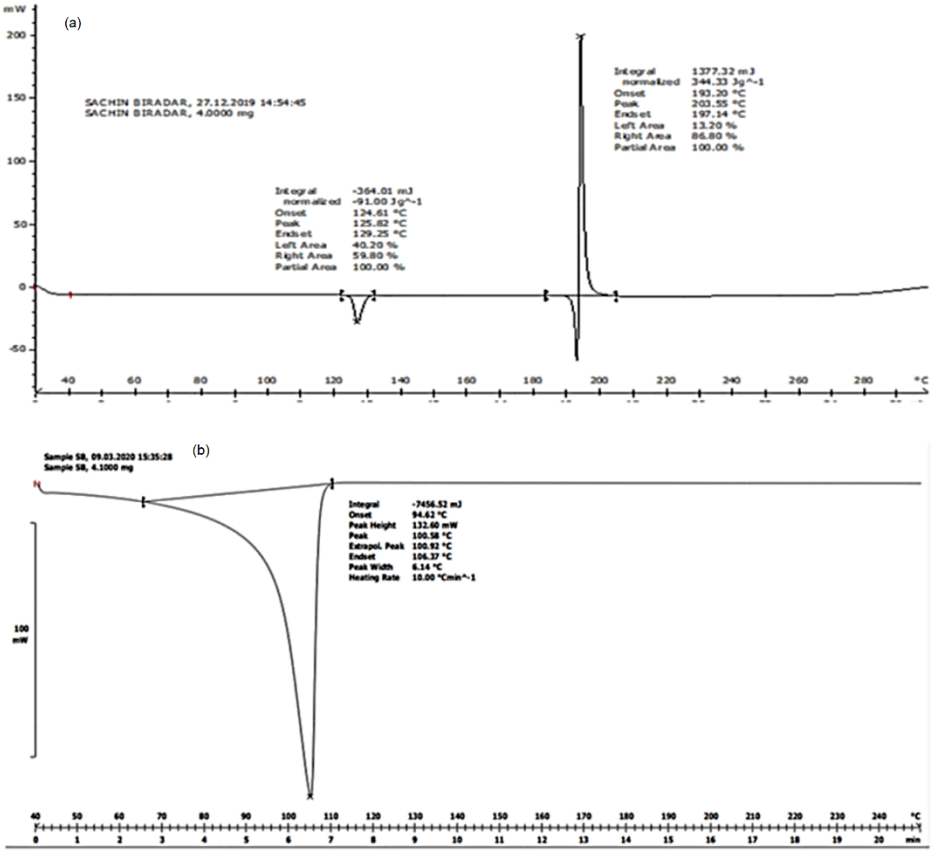

Figure 3. DSC thermograms of topiramate (a) and optimized MUPS formulation (b).

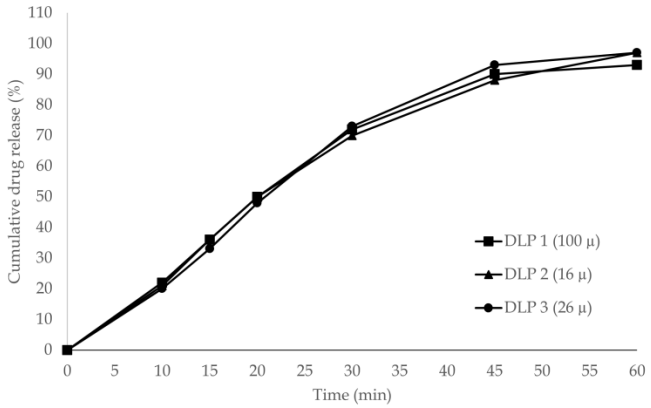

Figure 4. Effect of drug particle size on dissolution of topiramate MUPS formulations.

To select a suitable solvent system for taste masking polymer, different ratios of acetone and ethanol combination to get a 5% concentration of cellulose acetate were used and the final appearance of the resultant solutions are presented in Table 2. Acetone and ethanol alone didn't form clear solution of cellulose acetate. A combination of acetone-ethanol (80:20 v/v) gave a clear solution of cellulose acetate and hence this solution was used for coating of drug-loaded beads for taste masking.

Table 2. Selection of solvent ratio for solubilizing cellulose acetate.

Acetone (%)	Ethanol (%)	Appearance
100	Nil	Hazy suspension
Nil	100	Hazy suspension
90	10	Nearly clear solution
10	90	Hazy suspension
80	20	Clear solution

The manufacturing of topiramate taste masked MUPS was done in three stages. In the first stage, the sugar spheres were coated with drug suspension in a suitable binder. In the second stage, the drug loaded spheres were coated with a mixture of taste masking and pore forming polymer. In the third stage, taste masked pellets were blended with suitable amount of talc and after this, they were filled in sachets. Different batches of MUPS with their composition and batch codes are given in Table 3.

In the first stage, the effect of different concentrations of binder on drug loading was evaluated. In the second stage, the ratio of taste-masking and pore-forming polymers to acheive complete taste masking and desired release profile was optimized, In the third stage, optimization of quantity of talc was carried out, as talc makes the formulation hydrophobic.

The effect of binder on drug loading in the MUPS is shown in Table 4. Increase in the binder concentration increased the efficiency of drug-loading. At lower povidone concentrations, overages were loaded to achieve desired weight.

The results of optimization studies to finalize the ratio of taste masking polymer-pore forming polymer, the effect of concentration of taste masking polymer on the drug release and determination of concentration of talc are given in Figure 5. The effect of the ratio of taste masking polymer and pore former on drug release is given in Figure 5a. The batch of MUPS with cellulose acetate and povidone ratio of 2:1 was found to exhibit a gradual release patter, rather than a burst immediate release, which was considered as a better release profile and hence, this was selected as suitable ratio.

The effect of taste masking polymer concentration (in terms of weight gain of MUPS) on the dissolution of MUPS is shown in Figure 5b. Also, in the taste masking panel, all the volunteers recorded not more than 4 score for the taste masked pellets. Based on the results, the taste masking coating of 5% w/w was considered as optimum.

Table 3. Optimization of various formulation parameters used in the manufacturing of topiramate taste masked MUPS.

Batch Code	Optimization of Binder (PVP K-30) (%)	Optimization of taste masking polymer – pore former ratio (Cellulose acetate: Povidone)	Optimization of taste masking range (w/w)	Optimization of talc (%)
TSMP1	12.5	2:1	5.5	0.22
TSMP2	**25**	2:1	5.5	0.22
TSMP3	19.5	2:1	5.5	0.22
TSMP4	25	1:2	5.5	0.22
TSMP5	25	**2:1**	5.5	0.22
TSMP6	25	1:1	5.5	0.22
TSMP7	25	2:1	4	0.22
TSMP8	25	2:1	**5.5**	0.22
TSMP9	25	2:1	6.2	0.22
TSMP10	25	2:1	10.5	0.22
TSMP11	25	2:1	5.5	Nil
TSMP12	25	2:1	5.5	**0.22**
TSMP13	25	2:1	5.5	0.44
TSMP14	25	2:1	5.5	0.66

Table 4. Effect of binder concentration on drug loading in topiramate MUPS.

Batch Code	Binder Concentration	Drug Loading (%)
TSMP1	12.5	77
TSMP2	25	87
TSMP3	19.5	83

The results of determination of suitable concentration of talc are given in Figure 5c. The presence of talc in different ratios in formulations had no significant impact on dissolution and physical parameters. But the absence of talc in the formulation led to twinning of the pellets. Based on the results, the talc at 0.22%w/w was selected as optimized concentration.

After optimization of binder, taste masking polymer, ratio of taste masking polymer – pore former and concentration of talc, the optimized formula used for the topiramate MUPS is given in Table 5. MUPS with three different dose levels of topiramate were formulated and for these three sets of formulations, the optimization of process parameters was done at the drug loading stage and taste masking stage. The optimized values are given in Table 6.

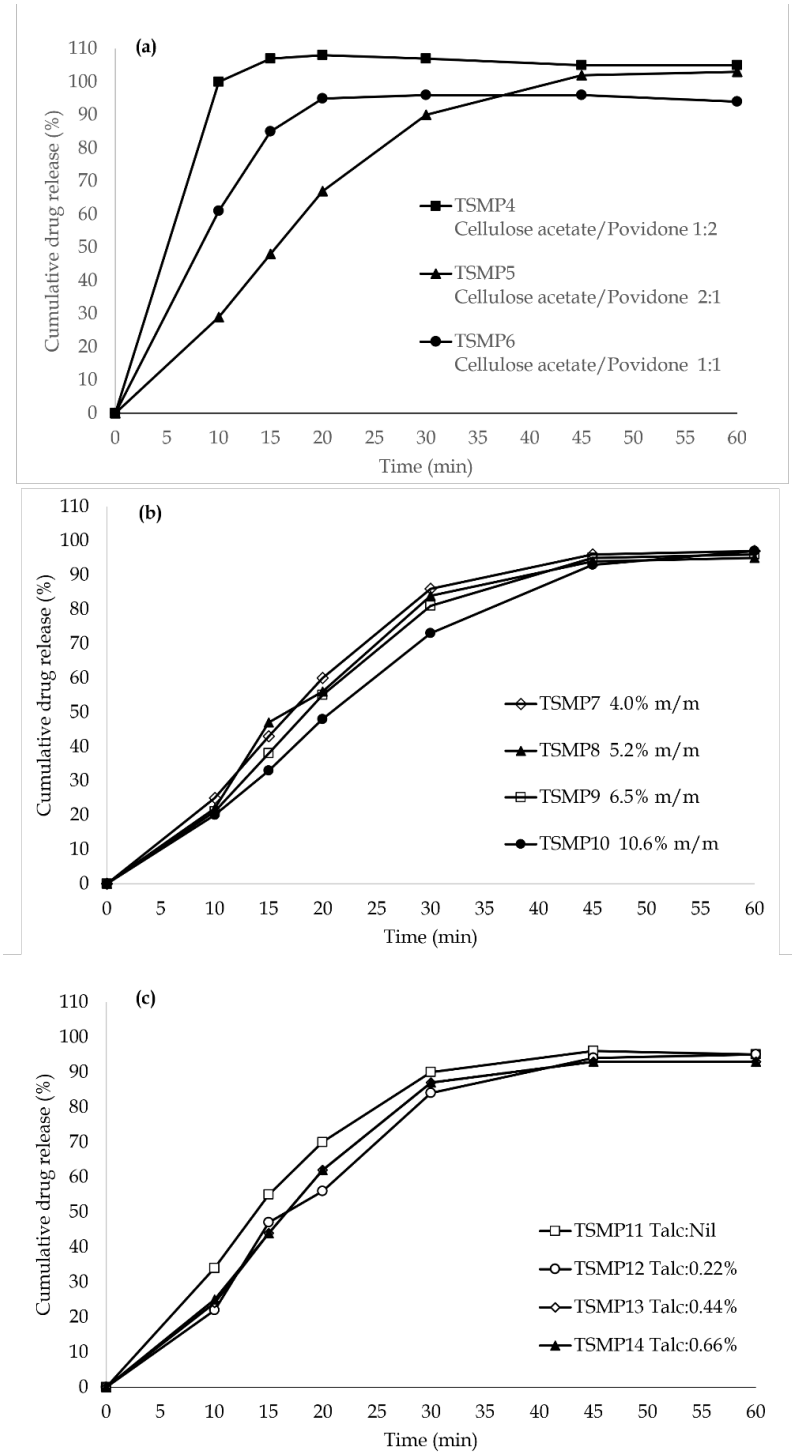

Figure 5. Effect of different formulation variables on the dissolution of topiramate from different batches of taste masked MUPS. (a) effect of ratio of cellulose acetate-povidone on dissolution; (b) effect of concentration of taste masking polymer concentration (in terms of weight gain) on dissolution; (c) effect of concentration of talc on dissolution.

Table 5. Optimized unit formula for topiramate taste masked MUPS.

Stage	Ingredients	Quantity used (mg) per sachet for drug dose level of		
		15 mg	25 mg	50 mg
Drug loading	Sugar Spheres	45	75	150
	Topiramate	15	25	50
	Povidone solution in purified water	25%	25%	25%
Taste masking	Cellulose acetate	2.25	3.75	7.5
	Povidone K30	1.05	1.75	3.75
	Acetone	qs	qs	qs
	Ethanol	qs	qs	qs
Lubrication	Talc	0.15	0.25	0.5
	Total	67.2	112	224

Table 6. Optimized process parameters for drug loading and taste masking stages of manufacture of topiramate taste masked MUPS.

Parameter		Observed values for drug loading	Observed values for taste masking
Inlet temperature (°C)	Min	53	36
	Max	67	42
Bed temperature (45 ± 5 °C)	Min	43	30
	Max	49	32
Exhaust temperature (°C)	Min	36	28
	Max	43	30
Atomization (kg/cm^2)	Min	2	02
	Max	3	03
Peristaltic pump (rpm)	Min	2	15
	Max	15	45
Blower drive (rpm)	Min	1500	2000
	Max	1900	2200
Air flow (CFM)	Min	923	1127
	Max	1122	1276
Spray rate (g/min)	Min	16	105
	Max	135	330
Total spraying time (min)		851	352

The assay of drug in the drug loaded MUPS was found to be 100.3% and in the taste masked MUPS was found to be 100.1%. The residual solvents ethanol and acetone were found to be 468 and 688 ppm.

The *in vitro* drug release profiles from various batches of MUPS in different media (multimedia dissolution) are given in Figure 6(a, b, c), corresponding to 15, 25 and 50 mg of topiramate, respectively. Media of pH 1.2, 4.5 and 6.8, were used to find out the effect of pH on drug release. It was ascertained by calculating similarity and dissimilarity factors (f2 and f1 factors) [13]. In all three doses of the drug, the release was found to be similar in all the three selected pH values (Table 7). Hence, by considering the simplicity of preparation and discriminatory nature, the medium of pH 1.2 (0.1 N HCl) was selected as suitable for dissolution of topiramate MUPS. From all the above studies, taste masked MUPS containing 50 mg topiramate was considered as optimized batch and was selected for short term stability study to assess the effect of storage conditions on the physicochemical and release properties of MUPS.

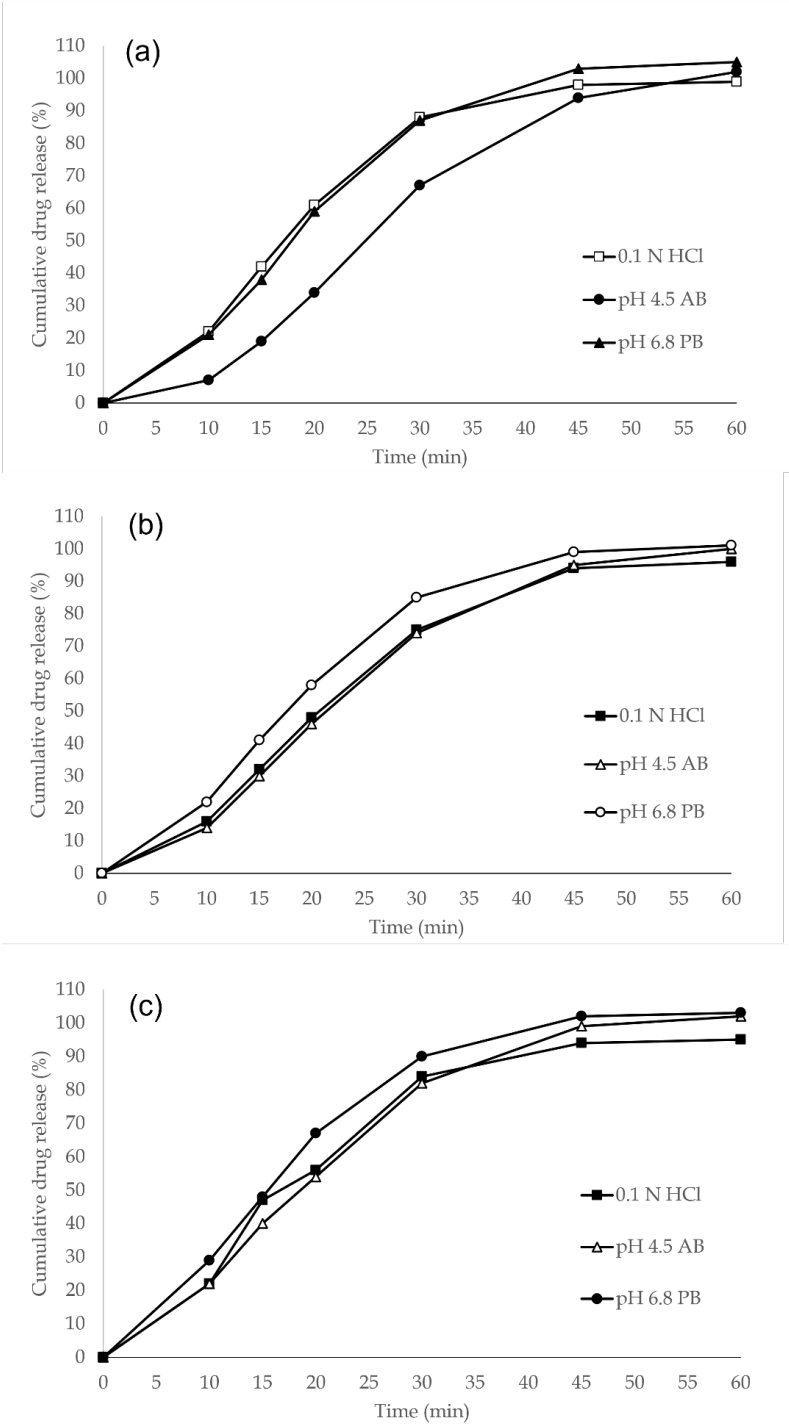

Figure 6. *In vitro* dissolution of topiramate from taste masked MUPS in media of different pH; (a) 15 mg dose; (b) 25 mg dose; and (c) 50 mg dose of topiramate

Table 7. Values of similarity factor f2 and dissimilarity factor f1 for the release of topiramate from taste masked MUPS in different media of pH 1.2, 4.5 and 6.8.

Media	Similarity factor (f2)			Dissimilarity factor (f1)		
	15 mg dose	25 mg dose	50 mg dose	15 mg dose	25 mg dose	50 mg dose
pH 1.2 and pH 4.5	31	81	66	23	3	6
pH 1.2 and pH 6.8	71	55	56	5	12	10

Short-term stability studies (at 40±2°C /75±5% RH for 6 months) on the promising formulation (50 mg topiramate containing MUPS) [22, 24] have shown no significant changes in physical appearance, drug content and *in vitro* drug release of MUPS containing 50 mg topiramate throughout the stability study period (Tables 8 and 9).

Table 8. Stability study data of taste masked MUPS containing 50 mg topiramate [22, 24].

Parameters	Initial	At the end of 3 months	At the end of 6 months
Physical appearance	White to off white	No Change	No Change
Water (By KF)	2.07	2.58	2.24
Drug assay	99.1	98.8	97.2
Topiramate related compound A	0.01	0.02	0.04
Individual unspecified degradation product	0.01	0.01	0.01
Total impurities	0.02	0.03	0.05
Limit of sulfate	0.02	0.03	0.07
Limit of sulfamate	0.01	0.01	0.03

Table 9. Dissolution profile of taste masked MUPS containing 50 mg topiramate in 0.1 N HCl (pH 1.2) during the stability study.

Time (min)	Cumulative drug release (%)		
	Initial	At the end of 3 months	At the end of 6 months
10	24	19	28
20	56	55	57
30	81	83	81
45	97	97	94
60	97	98	95

3. CONCLUSION

Topiramate loaded MUPS were produced by using cellulose acetate, povidone, taste masking and pore forming polymers. The influence of binder, particle size and coating ratios on the drug release profiles was systematically assessed. Except for the particle size of the API, all other parameters had tremendous influence on the taste masking and dissolution behavior of topiramate. The binder exhibited high percentage drug loading, and satisfactory drug release. Overall, the formulated topiramate loaded MUPS can open a new avenue for the delivery of therapeutics with improved potential for taste masking.

4. MATERIALS AND METHODS

4.1. Materials

Topiramate used in the research was a generous gift from Aurobindo Pharma Ltd. Hyderabad, India. Sugar spheres USNF (Pharma - spheres™ pellets neutral, 710-850 µm) were obtained from Werner GmbH, Germany. Povidone USP (PVP K-30) was obtained from BASF, Germany, and Cellulose Acetate USNF was purchased from Eastman Chemical Company, India. Talc USP was a generous gift sample from Imerys Talc, Italy. All other chemicals used were of analytical grade.

4.2. Methods

4.2.1. Determination of Crystallinity of API (Active Pharmaceutical Ingredient)

To study the effect of processing parameters on the physical state of drug (*i.e.* crystalline or amorphous), X-ray diffraction study of topiramate standard, was carried out using X-ray powder diffractometer (D8 Advance Davinci, Bruker, Germany) [15, 16].

4.2.2. Solubility of API

Saturation solubility studies were performed for topiramate. Solubility studies were performed in the physiological pH range of 1.2, 4.5, 6.8 and in Purified water (pH-7.0). Topiramate was added into 100 ml of

the designated media under stirring and was added periodically based on the solubilization in media. This experiment was continued for 24 h under stirring.

4.2.3. Drug-Excipient Compatibility Studies

All the selected excipients were subjected to compatibility studies with topiramate at 40°C, 75% RH in open condition for 1 month, followed by FTIR peak matching. The spectra of drug and excipient mixture were compared with that of the original spectra.

4.2.4. DSC (Differential Scanning Calorimetry)

DSC was performed using DSC 60A calorimeter to study the thermal behavior of the drug and to determine any incompatibility between drug and excipients. The samples were excited in hermetically conserved aluminum pans under nitrogen flow (30 mL/min) at the scanning rate of 40-200°C/min from 500-3000°C.

4.2.5. Effect of Particle size of API on Dissolution

Particle size of the API has impact on the process and on the release characteristics of the API from the dosage form. Three different batches of topiramate with different particle size were evaluated to study the impact of particle size. Each batch of the API was loaded onto the sugar spheres using fluid bed processor and the drug-loaded pellets were evaluated for dissolution.

4.2.6. Selection of Suitable Solvent System for Taste Masking Polymer [17, 18]

The manufacturing process involves fluid bed or Wurster process and this study was carried out to select a suitable solvent that dissolves the taste masking polymer completely to form a clear solution. Based on the chemical nature of the polymer and to minimize the exposure to solvents, class III solvents (acetone and ethanol) were evaluated in different combinations.

4.2.7. Manufacturing Process [19]

Fluid bed coating was selected for drug loading as well as taste masking. The steps involved in this method include drug loading, taste masking, sifting blending and sachet filling.

Drug Loading (Stage I): The required quantity of purified water was transferred into a suitable vessel with stirrer. Povidone was added under stirring and the stirring was continued upto 15 min to get clear solution. Topiramate was added to the above solution under stirring and mixture was stirred continuously for about 60 min to get homogenous suspension. This suspension was kept under mild agitation during coating. Sugar spheres were sifted through 1000 µm sieve (ASTM mesh no #18) and the retains were discarded. Sugar spheres were loaded in to Wurster coater (bottom spray fluidized bed processor) with minimum fluidization for pre warming with a target bed temperature of 45°C ± 5°C. Drug loading process was started once bed temperature of 45°C ± 5°C was achieved and 100% w/w of drug suspension was sprayed. After completion of spraying, pellets were dried at a bed temperature of 40° ± 5°C with minimum effective fluidization to get the loss of drying not more than 2.0% w/w when checked by IR moisture analyzer in auto mode at 105°C. Drug loaded pellets (#18 sieve passed and #30 sieve retains) were shifted into suitable container. Assay of the drug in the drug-loaded pellets and taste masked pellets was done by HPLC.

Taste Masking (Stage II): Acetone and ethanol mixture (80:20) was prepared under constant stirring. Cellulose acetate was added to this mixture under stirring for about 10 min. Povidone was added under stirring and stirring was continued for 45 min to get a clear solution. Drug loaded pellets [17, 20] were loaded into Wurster coater (bottom spray fluidized bed processor) and pre warming was done with minimum fluidization with a target bed temperature of 30°C±5°C. Spraying of the taste masking solution was done till desired weight gain was achieved (9% w/w). After completion of spraying, taste masked pellets were dried at a bed temperature of 40° ± 5°C with minimum effective fluidization to get the loss on drying not more than 2.0% w/w when checked by IR moisture analyzer in auto mode at 105°C. Taste masked pellets (#18 sieve passed and #30 sieve retains) were shifted into suitable container.

Sifting and Blending (Stage III): Talc was sifted through 250 µm sieve (ASTM mesh no # 60). Taste masked pellets and sifted talc was loaded into low shear blender (Rimek, Double Cone Blender) and lubricated for 5 min.

4.2.8. Optimization of Binder

Binder has an important role to play in the MUPS dosage forms. Binder ensures that the drug is totally loaded onto the sugar spheres without any loss of drug during the fluid bed process. The concentration of binder should be sufficient to ensure that the drug loading solution has enough binding efficiency to give appropriate drug loading. Binder also has a significant effect on drug release profile from pharmaceutical dosage forms. In the present study, the effect of binder concentration on the drug loading efficiency was evaluated.

For the preparation of drug-loaded pellets, an accurately weighed quantity of povidone was dissolved into the required quantity of purified water in a suitable vessel to get a clear solution. Accurately weighed quantity of topiramate was added to the povidone solution with continuous stirring to form a clear suspension without foaming and lump formation. The resultant drug suspension was sprayed over the sugar spheres [21].

4.2.9. Optimization of Taste Masking Polymer and Pore Former Ratio [22]

Cellulose acetate, which is an insoluble polymer, is selected as a taste masking polymer. Due to the insoluble nature of the cellulose acetate a pore former is used at a suitable concentration to achieve the desired release profile. The release profile should be like any immediate release product without any retardation in the drug release. Povidone was used as a pore former. The concentration of the povidone plays a critical role to ensure the drug release from the taste masked pellets uniformly.

The drug loaded sugar spheres were coated with different ratios of (cellulose acetate and povidone) taste masking solution to achieve the desired release profile and taste masking effect. Briefly, required quantities of acetone and ethanol in the ratio of 80: 20 were transferred into a suitable vessel. Cellulose acetate was added under stirring until a clear solution was formed. Then, povidone was added to the same solution while stirring until a clear solution was formed. The resulting solution was passed through 250 µm sieve (ASTM mesh # 60) and sprayed over drug-loaded spheres.

4.2.10. Determination of Optimum Taste Masking Range

The percentage of coating required to mask the bitter taste of topiramate was evaluated. This was required to balance both the requirements of taste masking and drug release from the taste masked pellets. Sensory evaluation of the taste of formulations was carried out by six healthy volunteers, who were asked to keep the pellets in mouth for 10 seconds, spit off and rate the bitterness as per the scale. A numerical scale between 0-10 was used, in which 0 indicated absence of bitterness and 10 indicated maximum bitterness [3, 4].

4.2.11. Optimization of Talc

Talc is added into the formulation to avoid twining or doublets in the process and to have a continuous unhindered process. Talc also helps in preventing the formation of lumps of pellets. The final optimized formulation was further taken to establish various process parameters at higher scale and to confirm the reproducibility of the proposed composition. Scale up batch was evaluated in 125 L fluid bed processor. Batch size: 22.4 kg for 50 mg strength, 11.2 kg for 25 mg strength and 6.72 kg for 15 mg strength.

4.2.12. Process Optimization [19, 23]

Various Fluid bed process equipment parameters such as inlet temperature, bed temperature, exhaust temperature, atomization, rpm of peristaltic pump, air flow and spray rate were evaluated and optimized for drug loading stage and taste masking stage. The process optimization for drug loading and taste masking steps was done following the procedures described earlier under the heading 'Manufacturing process'.

4.2.13. Dissolution Study in Media of Different pH (Multi-media Dissolution) [24]

Dissolution study of the optimized composition was carried out across the physiological pH (pH 1.2 to 6.8). The dissolution study of taste masked MUPS was carried out in 900 mL of different dissolution media using type I dissolution apparatus (Basket) at 100 rpm. The temperature of the dissolution media was maintained at 37±0.5°C. Sampling was done in six replicates at predetermined intervals. The same volume of fresh dissolution medium was replaced after each sampling to maintain the sink condition. The samples were analyzed using HPLC [22].

4.2.14. Stability Studies [12]

Short-term stability studies on the optimized formulation were carried out for a period of six months at 40±2°C / 75±5% RH. Changes in physical appearance, drug content and in vitro dissolution were noted initially and after 3- and 6-months intervals.

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