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RESEARCH ARTICLE

PREFORMULATION STUDY IN THE DEVELOPMENT OF A TABLET FORMULATION FOR THE TREATMENT OF ULCERATIVE COLITIS

Khemchand Gupta, S.B. Roy, Indrajeet Singhvi

Pacific College of Pharmacy,
Pacific Academy of Higher Education and Research University, Udaipur-313024, Rajasthan, India.
E-mail: khem_pharma@yahoo.co.in

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Abstract:
Ulcerative colitis (UC) is one of the inflammatory bowel diseases that lead to formation of ulcers or sores with inflammation along the inside of the colon. The sores generated found to interfere with the normal digestive or physiological processes. Drug administration through oral cavity is still highly preferred route in case of chronic conditions where frequent dosing is required. Most of conventional formulations used in colon diseases showed low efficacy associated with limited entry of drug at the site of action. Therefore amount and rate of drug that reaches the site of action is the key factor in the management of UC. The selection of drug depends on its physicochemical properties along with its compatibility with excipients to be used in the formulation. Therefore, the present research was aimed to study the preformulation parameters for selected drug (Mesalamine) along with its compatibility profile. This data could help in development of the site specific drug delivery system for an effective treatment of UC. In preformulation studies several parameters have been investigated such as solubility, particle size, density, flowability, assay and loss on drying content and drug-excipient compatibility. Mesalamine was found to be compatible with excipients used in formulation. The drug showed good flowability as well as considerable stability.

Keywords: Preformulation, Targeted, Mesalamine, Ulcerative Colitis

Introduction
UC is one of the inflammatory bowel diseases that lead to formation of ulcers or sores with inflammation along the inside of the colon. The sores generated found to interfere with the normal digestive or physiological processes. This chronic inflammatory condition with indistinct cause found to affect the colon, commonly the rectum and proximally extends in a continuous fashion. Generation of a humoral immune profile has been observed that was associated with dominance of mucosa in UC patients by CD4+ non-T helper lymphocytes. The flawed colonic mucosa causes the entry of luminal bacterial and dietary products to the mucosa. It has been reported that an intestinal inflammation get developed due to the presence of luminal bacteria along with absence of regulatory proteins in the mucosal immune system.

Presently, 5-aminosalicylic acids (ASAs) provide the best line of treatment in UC patients for maintaining the remission at mild-to-moderate level. It has been reported that the regression in disease severity could be observed in patients taking oral 5-ASAs regularly than those who do not. Moreover, mild-to-severe patients not responding to 5-ASA can be switched to other options like immune-modulating agents, corticosteroids and biotherapy. Further, it has been reported that surgery cannot be avoided in one-third of UC patients during their diseased state. However, treatment anticipation from patients' point of view could be understood efficiently due to advancement in diverse therapies[1]. Therapy on UC is majorly directed towards the reduction of symptoms in UC patients and sustain at lower level for longer period of time.

Further, it has been reported that use of 5-ASA in management of UC could results in reduction of chances in development of colorectal cancer [2].Mesalazine, a drug from ASA category is commonly used as standard treatment in UC attributed to its safety and efficacy profiles. ASAs given orally in UC patients showed comparable pharmacokinetic profiles although they are available in variety of dosage forms exhibiting diverse release profiles.[3,4] However, in chronic conditions where frequent dosing is required, oral route is highly preferred for drug administration. Most of conventional formulations used in colon diseases showed low efficacy associated with limited entry of drug at the site of action. Therefore, the present research was aimed to study the preformulation parameters for Mesalamine together with its compatibility profile with the excipients to be used in the formulation development.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (MCC) from FMC Biopolymer (Signet), India; Hydroxypropyl Cellulose (HPC), Hyroxypropyl methylcellulose (HPMC) and Sodium starch glycolate (SSG) from Signet Chemicals Ltd, Mumbai, India; Aerosil 200 from Degussa Antwerpen Tysmanstunnel West, Antwerpen, Belgium; Magnesium stearate from Amishi drugs & chemicals, Ahmedabad, India; Polyvinyl pyrrolidone K30 (PVP K30) from ISP Technology, NJ, USA; Talc from Amishi drugs & chemicals, Ahmedabad, India; Eudragit S100 from Evonik Industries, Mumbai, India; Acetyl tributyl citrate, Titanium dioxide and Ferric oxide red from ROHA dychem Pvt. Ltd., Mumbai, India; Film coating colour from Colorcon Asia Pvt. Ltd., Verna, Goa were purchased. All other chemicals used were of analytical grade.

Methods

Preformulation Study of Drug

Preformulation investigations were designed to identify those physicochemical properties and excipients that may influence formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of resulting product. Preformulation study was accomplished by testing the drug for various parameters as described below.

Solubility

The solubility of drug was determined in various mediums such as water (pH 7.0), 0.1N HCl (pH 1.2), acetate (pH 4.5) and phosphate buffer (pH 6.8 and pH 7.2).

Particle size

Particle size of drug was determined by Malvern particle size analyzer which is based on principle of light scattering. The particles were analyzed by two methods: Dry and Wet method[5].

Bulk density

An accurate quantity of drug (25 g) was weighed, which was previously passed through 20 # sieve and transferred in 100 mL graduated cylinder. The level of powder bed was carefully adjusted without compacting, and unsettled apparent volume (V_0) was recorded. Further apparent bulk density (g/mL) was calculated by following formula (Equation 1),

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}} \quad \ldots(1)$$

Tapped density

An accurate quantity of drug (25 g) was weighed, which was previously passed through 20 # sieve and transferred in 100 mL graduated cylinder. Then cylinder containing sample was mechanically tapped by raising it and allowing it to drop under its own weight using mechanically tapped density tester. The tester provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 100 times initially and tapped volume (V_1) to the nearest graduated units was measured. The tapping was repeated for an additional 200 times and tapped volume (V_2) to the nearest graduated units was recorded. Further tapped density (g/mL) was calculated by following formula (Equation 2),

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}} \quad \ldots(2)$$

Carr's compressibility index & Hausner's ratio

Compressibility index and Hausner's ratio were measured of propensity of powder to be compressed. The standard scale of flowability is given in Table 1. These parameters were calculated by using following formula (Equation 3 and Equation 4),

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \ldots(3)$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \ldots(4)$$

Angle of repose

The frictional force in powder and ultimately its flowability can be measured by angle of repose. The relation between measure of flowability and angle of repose is given in Table 1. Angle of repose was measured by fixed funnel method and was calculated by using following formula (Equation 5),

$$\text{Tan } \theta = \frac{h}{r} \quad \ldots(5)$$

Where, h = Height of heap in cm and r = Radius of heap in cm.

Drug-excipients compatibility study
The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation.

In this method different excipients were selected and mixed separately with drug in proportion generally used for tablet formulation. Three sets of each mixture were prepared, from which one set was used for initial analysis while two sets were kept at room temperature and 50°C/80 % RH (relative humidity) for one month. After one month samples were observed visually for change of color or its appearance in powder form. Relative substances were also checked for measurement of impurity concentration.

RESULTS AND DISCUSSION

Preformulation Study of Drug
Preformulation studies were first step in rational development of dosage form of a drug substance. The objectives of preformulation studies were to develop a portfolio of information about drug substance, so that this information was useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Physicochemical Properties
Physical description
Mesalamine is an off white to Rose light brown crystalline powder.

Aqueous solubility (as function of pH):
Solubility of Mesalamine and Omeprazole
Mesalamine was observed to have maximum solubility in 0.1 N HCl and increases from pH 4.5 to pH 7.5 range. However solubility of Omeprazole increases with increase in pH (Table 2).

Melting range of Mesalamine:
Melting point of Mesalamine was found at 283 ºC which was in accordance with previously reported results.

Flow properties of Mesalamine and Omeprazole
Mesalamine has poor flowability and very low bulk density. The data of Angle of Repose, Carr's Index and Hausner's Ratio indicated poor flow property of both Mesalamine and Omeprazole (Table 3).

Drug–Excipient compatibility study
The drug-excipient compatibility was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation. Results for drug-excipient compatibility testing for both drugs (Mesalamine and Omeprazole) are given in Table 4 to Table 7.

Assay content
Assay content of Mesalamine and Omeprazole was found to be within the acceptable limits (Table 8).

Impurities
Omeprazole API
Impurity profile of Omeprazole was found to be within the prescribed standards (Table 9).

Loss on Drying (LOD)
LOD of Mesalamine and Omeprazole was observed within the specified criteria (Table 10).

CONCLUSION

ASA agents will continue to retain their first choice in management of UC and restraining it at mild to moderate level. Several developments in the formulation over the years made use of these agents in effective and tolerable treatment of UC. Mesalamine (a 5-ASA agent) is more tolerable API compared to its predecessor drug sulfasalazine. In the present study, drug was found to be compatible with excipients used in the formulation development. The pure drug exhibited good flowability, micromeritics as well as considerable stability tested at set of conditions as per ICH guidelines.

References

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Table 1. Scale of flowability.

Flow Character	**Compressibility Index (%)**	**Hausner's Ratio**	**Angle of repose (θ)**
Excellent	≤ 10	1.00–1.11	25-30
Good	11–15	1.12–1.18	31-35
Fair (Aid not needed)	16–20	1.19–1.25	36-40
Passable (May hang up)	21–25	1.26–1.34	41-45
Poor (Must agitate or vibrate)	26–31	1.35–1.45	46-55
Very poor	32–37	1.46–1.59	56-65
Very very poor	>38	>1.60	> 66

Table 2. Solubility of Mesalamine and Omeprazole at different pH.

Media	**Mesalamine (mg/mL)**	**Media**	**Omeprazole (mg/mL)**
0.1 N HCl	18.2	pH 6.8 phosphate buffer	0.1363
pH 4.5 buffer	2.7	pH 8.0 tris buffer	0.1875
pH 6.0 buffer	3.7	pH 10.0 borate buffer	1.0717
pH 7.2 buffer	8.4		
pH 7.5 buffer	9.7		

Table 3. Micromerits of Mesalamine and Omeprazole.

Drug	**Particle size**	**Density**		**Flow property**		
	D (0.9) microns	**Bulk Density (g/cm^3)**	**Tapped Density (g/cm^3)**	**Carr's Index (%)**	**Hausner's Ratio**	**Angle of Repose (θ)**
Mesalamine	38.65	0.18	0.260	25.000	1.333	40.43
Omeprazole	15.12	0.270	0.360	25.000	1.333	38.43

Table 4: Data of drug–excipient compatibility study for Mesalamine- *Related substances data at initial stage.*

Ingredient	**Ratio**	**MAN-1**	**3-ASA**	**Maximum unknown (specify RRT)**	**Total Impurities**
Mesalamine API (Compacted)	NA	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Methacrylic Acid Copolymer (Type B)	5:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Methacrylic Acid Copolymer (Type A)	5:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Hypromellose	5:1	ND	ND	0.06% (RRT-1.58)	0.08%
Mesalamine API + Talc	5:1	ND	ND	0.05% (RRT-0.11)	0.07%
Mesalamine API + Magnesium Stearate	10:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Colloidal Silicon Dioxide	10:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Microcrystalline Cellulose	5:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Lactose	5:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + PEG 6000	5:1	ND	ND	0.01% (RRT-0.33)	0.01%
Mesalamine API + Iron Oxide Red	10:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Sodium Starch Glycolate	5:1	ND	ND	0.01% (RRT-0.33)	0.01%
Mesalamine API + Triethyl Citrate	10:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API + Titanium Dioxide	10:1	ND	ND	0.02% (RRT-0.33)	0.02%
Mesalamine API +PVPK 30	5:1	ND	ND	0.04%	0.04%
Mesalamine API + ATBC	5:1	ND	ND	0.04%	0.05%

API : Active pharmaceutical ingredient
MAN-1 : 2- hydroxyl-5-nitro benzoic acid
3-ASA : 3- amino salicylic acid
ND : Not detected
PEG : Polyethylene glycol

ATBC : Acetyl tri-*n*-butyl citrate

Table 5. Drug-excipient compatibility study for Mesalamine - *Related substances data at 45°C / 75%RH/ 1M.*

Sample	**Ratio**	**MAN-1**	**3-ASA**	**Maximum unknown (specify RRT)**	**Total Impurities**
Mesalamine API (Compacted)	NA	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Methacrylic Acid Copolymer (Type B)	5:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Methacrylic Acid Copolymer (Type A)	5:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + HPMC	5:1	ND	ND	0.05%(RRT-0.30)	0.05%
Mesalamine API + Talc	5:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Magnesium Stearate	10:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Colloidal Silicon Dioxide	10:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Microcrystalline Cellulose	5:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Lactose	5:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + PEG 6000	5:1	ND	ND	0.09%(RRT-0.30)	0.10%
Mesalamine API + Iron Oxide Red	10:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Sodium Starch Glycolate	5:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Triethyl Citrate	10:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API + Titanium Dioxide	10:1	ND	ND	0.04%(RRT-0.30)	0.04%
Mesalamine API +PVPK 30	5:1	ND	ND	0.02%(RRT-0.36)	0.04%
Mesalamine API + ATBC	5:1	ND	ND	0.04%(RRT-0.38)	0.04%

Table 6. Drug-excipient compatibility study for Mesalamine - *Physical condition at 45°C / 75% RH/ 1M.*

Sample	**Description**	***Observations 45°C / 75% RH/ 1M***
Mesalamine API (Compacted)	Light tan to pink colored powder material	No change
Mesalamine API + Methacrylic Acid Copolymer (Type B)	Light tan to pink colored powder material	No change
Mesalamine API + Methacrylic Acid Copolymer (Type A)	Light tan to pink colored powder material	No change
Mesalamine API + HPMC	Light tan to pink colored powder material	No change
Mesalamine API + Talc	Light tan to pink colored powder material	No change
Mesalamine API + Magnesium Stearate	Light tan to pink colored powder material	No change
Mesalamine API + Colloidal Silicon Dioxide	Light tan to pink colored powder material	No change
Mesalamine API + Microcrystalline Cellulose	Light tan to pink colored powder material	No change
Mesalamine API + Lactose	Light tan to pink colored powder material	No change
Mesalamine API + PEG 6000	Light tan to pink colored powder material	No change
Mesalamine API + Iron Oxide Red	Red colored powder material	No change
Mesalamine API + Sodium Starch Glycolate	Light tan to pink colored powder material	No change
Mesalamine API + Triethyl Citrate	Light tan to pink colored powder material	No change
Mesalamine API + Titanium Dioxide	Light tan to pink colored powder material	No change
Mesalamine API +PVPK 30	Light tan to pink colored powder material	No change
Mesalamine API + ATBC	Light tan to pink colored powder material	No change

Table 7. Data of Drug–excipient compatibility study for Omeprazole.

Sample	Ratio	Description		Observation of Total Impurity	
		Room Temperature	50^0C/80% RH 30 Days	Room Temperature	50^0C/80% RH 30 Days
Omeprazole	--	White to off white powder	White to off white powder	0.03	0.04
Omeprazole: Pregelatinised starch	1: 10	White to off white powder	White to off white powder	0.05	0.06
Omeprazole: Lactose	1: 10	White to off white powder	White to off white powder	0.04	0.04
Omeprazole: SLS	1: 5	White to off white powder	White to off white powder	0.04	0.04
Omeprazole: HPC	1: 5	White to off white powder	White to off white powder	0.05	0.06
Omeprazole: Mg Hydroxide	1: 5	White to off white powder	White to off white powder	0.05	0.05
Omeprazole: Talc	1:1	White to off white powder	White to off white powder	0.04	0.04
Omeprazole: Mg stearate	1:1	White to off white powder	White to off white powder	0.05	0.05
Omeprazole: HPMC	1: 0.5	White to off white powder	White to off white powder	0.05	0.06
Omeprazole: PVA	1:1	White to off white powder	White to off white powder	0.04	0.04
Omeprazole: Titanium dioxide	1:1	White to off white powder	White to off white powder	0.03	0.04
Omeprazole: HPMC phthalate 55	1:1	White to off white powder	White to off white powder	0.04	0.04
Omeprazole: HPMC phthalate 50	1:1	White to off white powder	White to off white powder	0.05	0.05
Omeprazole: Cetyl alcohol	1:1	White to off white powder	White to off white powder	0.04	0.05
Omeprazole: Sugar spheres	1:5	White to off white powder pellets mixture	White to off white powder pellets mixture	0.03	0.05

Table 8. Assay content of Mesalamine.

Drug	**Results**	**Acceptance criteria:**
Mesalamine	99.6%	98.0%–102.0% on the dried basis
Omeprazole	99.6%	98.0%–102.0% on the dried basis

Table 9: Impurity profile of Omeprazole.

Impurities	**Results**	**Acceptance Criteria, NMT (%)**
5-Methoxy-1H -benzimidazol-2-thiol	0.01	0.15
Omeprazole *N* -oxide (omeprazole related compound E)	0.01	0.15
Omeprazole sulfone *N* -oxide (omeprazole related compound I)	0.01	0.15
Desmethoxyomeprazole	0.01	0.15
Omeprazole	0.01	—
Omeprazole sulfone (omeprazole related compound A)	0.01	0.15
Omeprazole 4-chloro analog	0.01	0.15
Ufiprazole	0.01	0.15
Omeprazole thioxopyridoanalogs	0.01	—
Any other individual impurity	0.03	0.10
Total impurities	0.18	1.0

Table 10: LOD of Mesalamine.

Drug	**Results**	**Acceptance criteria**
Mesalamine	0.28%	NMT 0.5%
Omeprazole	0.30%	NMT 0.5%