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PREPARATION AND STANDARDIZATION OF SUPRAMOLECULAR COMPLEXES OF MONOAMMONIUM GLYCYRRHIZINATE (MASGA) WITH POORLY SOLUBLE DRUG SUBSTANCES AND THEIR INFLUENCE ON AQUEOUS SOLUBILITY, BIOAVAILABILITY, AND BIOLOGICAL ACTIVITY

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Abstract
Monoammonium glycyrrhizinate (MASGA) is a water-soluble amphiphilic saponin that forms stable supramolecular complexes with poorly soluble drug substances, whereas the parameters of their preparation and standardization have thus far been described only in a fragmentary manner [1–3,8,9,11–13]. This study systematizes existing data on the structure and self-assembly of glycyrrhizinates, substantiates the role of MASGA as a matrix-forming excipient and a "mild solubilizer," and demonstrates that complex formation with low-molecular-weight substrates (urea, thiourea, amino acids, cholesterol, and several pharmaceutical compounds) results in a multiple increase in aqueous solubility, accelerated dissolution, and enhanced bioavailability and biological activity [3,11–13,17–21,25,26,28].
A unified approach is proposed for the preparation of solid and semi-solid dosage forms based on MASGA, including mechanochemical co-milling, the solvent–evaporation method, lyophilization,and in situ self-assembly. Key criteria for their standardization are formulated: quantitative analysis of the components, control of stoichiometry and solid-state form, spectral "fingerprint," dissolution profile, and in vitro and in vivo activity indicators. Taken together, these elements form the foundation for QbD-oriented design and validation of MASGA complexes as a standardized excipient for the delivery of poorly soluble drugs. The numerical parameter ranges provided in Sections 3.3–3.3.6 represent preliminary estimates (design assumptions) based on literature data and are subject to refinement in targeted experimental studies.

Keywords: Monoammonium salt of glycyrrhizic acid (MASGA), disodium salt of glycyrrhizic acid (Na_2GA), supramolecular complexes, aqueous solubility, bioavailability, glycyrrhizic acid (GA), solubilization, standardization.

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Introduction

Glycyrrhizic acid (GA) is the main triterpenoid saponin of licorice roots (Glycyrrhiza spp.), consisting of glycyrrhetinic acid conjugated with a disaccharide fragment of glucuronic acid [1,4]. The amphiphilic nature of the molecule (a hydrophobic triterpenoid backbone + a hydrophilic sugar "head") determines its ability to self-associate, forming micelles and more complex supramolecular structures [1–3]. Classical studies by the schools of G.A. Tolstikov and L.A. Baltina, as well as subsequent reviews, have demonstrated that GA and its aglycone exhibit a broad spectrum of pharmacological activities, including anti-inflammatory, antiviral, hepatoprotective, immunotropic, and antitumor effects, among others [1–3,5–7]. The amphiphilic nature and self-assembling capability of GA naturally led to the concept of using it as a "natural carrier" for hydrophobic molecules. Studies by N.E. Polyakov and colleagues have demonstrated that GA forms stable inclusion complexes and micellar aggregates, significantly enhancing the solubility of both aromatic and aliphatic substrates and modulating their interactions with biological membranes [1,8,9,16].

Particular attention has been given to drug carriers based on GA salts. The disodium salt (Na_2GA) has been proposed as a matrix-forming foundation for solid dispersions and supramolecular delivery systems for antiparasitic and other poorly soluble drugs [10,11]. For Na_2GA complexes with praziquantel, fenbendazole, and several other active pharmaceutical ingredients, a multiple-fold increase in solubility and accelerated dissolution have been observed, accompanied by enhanced pharmacokinetic parameters (AUC, C_max) in vivo [11–13]. On this basis, GA-salt-based nanocomplexes, hydrogels, and hybrid materials are being developed for targeted anticancer and antiviral therapy [14–16]. In parallel, supramolecular complexes of GA with small biologically active molecules (such as salicylic acid, menthol, and flavonoids) have been investigated. For the GA–salicylic acid and GA–menthol systems, changes in acid–base properties, enhanced anti-inflammatory and antioxidant activities, as well as mitochondria-protective effects have been demonstrated [17–19]. GA compositions with flavonoids (e.g., quercetin) exhibit increased antibacterial and antihemolytic activities compared to the individual components [27], confirming the role of GA as a "functional carrier" that combines both pharmacophoric and supramolecular functions [3,8,17–19,27]. The monoammonium salt of glycyrrhizic acid (MASGA, glyciram) is a water-soluble ammonium glycyrrhizinate that has long been used in pharmaceutical practice in the post-Soviet countries [2,3]. Unlike Na_2GA, MASGA more readily forms various crystalline modifications and amorphous forms, is highly compatible with soft pharmaceutical formulations, and can simultaneously function as both an active ingredient and an excipient [2,3,20,21,26]. It has been shown that MASGA forms stable host–guest complexes with cholesterol, urea, thiourea, amino acids, and a number of pharmaceutical substances, altering their solubility, acid–base properties, and biological activity [17–21,25,26,28]. Ammonium glycyrrhizinate complexes with sulfonamides and other chemotherapeutic agents exhibit enhanced interferon-inducing and antimicrobial activities compared to the parent compounds [20,26]. At the same time, there are currently no unified approaches in the literature for the preparation, standardization, and pharmaceutical development of MASGA complexes with poorly soluble drugs. Streptocide (a sulfonamide) and sulfadimethoxine (sulfadimidine) are classic chemotherapeutic agents with low water solubility; their insufficient solubility limits bioavailability and necessitates high doses, thereby increasing the risk of side effects [14]. Enhancing the solubility and local activity of these drugs through complexation with

MASGA logically continues the approach established by the Na_2GA–praziquantel/fenbendazole systems [11–13]. The aim of this work is, based on an analysis of recent domestic (G.A. Tolstikov, L.A. Baltina, D.N. Dalimov, A.Kh. Khaitbaev, et al.) and international studies, to develop a conceptual model for the preparation and standardization of MASGA supramolecular complexes with streptocide, sulfadimethoxine, and other hydrophobic substances, aimed at enhancing their water solubility, bioavailability, and biological activity [1–3,5–7,11–13,17–21,24–26,28].

2. Materials and Methods

The article is an analytical review with elements of methodological generalization. As "materials," data from experimental studies in the following areas are considered:

- the structure and self-organization of GA and its salts [1–3,8,9,16];
- supramolecular complexes of Na_2GA with pharmaceutical substances [10–13];
- complexes of GA with small bioactive molecules [17–19,27];
- complexes of MASGA with urea, thiourea, amino acids, cholesterol, and pharmaceutical substances [20,21,25,26,28];
- analytical and metrological applications of MASGA [22,23].

Based on the analysis of these data, a unified approach has been developed for the preparation and quality control of MASGA complexes. Streptocide and sulfadimethoxine, representatives of Class II of the Biopharmaceutics Classification System (BCS), are considered as model poorly soluble drugs [14]. The carrier used is pharmacopeial MASGA, obtained from technical GA through a stepwise purification scheme [1–3,20,26].

2.1. Approaches to the Preparation of MASGA–Drug Supramolecular Complexes

Four basic synthesis routes for MASGA–drug complexes have been identified. These were selected by analogy with Na_2GA–drug systems and previously described glyciram complexes [10–13,17–21,25,26]:

1. Mechanochemical co-grinding**.** MASGA and the drug (molar ratio 1:1–10:1) are co-ground in a planetary ball mill at 300–400 rpm, with temperature controlled ≤40 °C. The conditions are identical to those used for Na_2GA–praziquantel and Na_2GA–fenbendazole systems [10–13]. Detailed parameters (mill type, cycle time, ball-to-powder ratio) are rationally provided in the Appendix.
2. Solution–evaporation method**.** MASGA and the drug are dissolved together in a water–alcohol mixture (~50% ethanol, 40 °C) followed by vacuum evaporation to obtain a glassy or fine-crystalline residue [10,17–19]. Specific evaporation and drying regimes are also conveniently documented in the Appendix.
3. Lyophilization. Concentrated aqueous solutions of MASGA complexes are frozen and subjected to sublimation drying, which allows the supramolecular structure to be "fixed" in the solid phase. This approach is widely used for glycyrrhizinate gel-based systems [10,14–16].
4. In situ self-assembly. Complexes are formed directly during the preparation of soft dosage forms (gels, sprays, suspensions): upon dissolution, MASGA forms micellar and fibrillar aggregates that incorporate drug molecules; the system can be further stabilized with polysaccharides or metal ions [14–16,22,23].

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For solid substances such as MASGA–drug, mechanochemical and solution–evaporation methods are considered as primary routes, while lyophilization and in situ self-assembly serve as auxiliary methods for soft and nanoscale formulations.

2.2. Analytical Methods and Standardization Parameters

The set of methods was selected with a view toward future pharmacopeial standardization [1–3,8–11,17–19,22,23,26]:

- Phase solubility analysis (Higuchi–Connors) and UV titration (Benesi–Hildebrand) for determining stoichiometry and stability constants;
- FTIR spectroscopy and NMR (^{1}H, ^{13}C, 2D-NOE) for confirming complex formation;
- DSC and XRPD for monitoring phase state;
- DLS and ζ-potential measurements for nanoscale systems [14–16,27];
- In vitro dissolution tests (USP II/IV) in media of varying pH [11–14];
- In vivo pharmacokinetic and pharmacodynamic evaluation, by analogy with Na_2GA carriers [11–13] and GA complexes with small molecules [17–19,27,28].

At the stage of designing regulatory documentation for MASGA–drug substances, the following Critical Quality Attributes (CQA) are proposed to be established in line with ICH Q6A [29,30]:

- Identification (spectral "fingerprint," chromatography);
- MASGA and drug content (HPLC/UV);
- Molar ratio of components;
- Residual solvents and moisture;
- Dissolution profile;
- Specific activity indicators (MIC, antioxidant and other markers) [14,17–20,24,28].

3. Results and Discussion

3.1. Structural Basis for Complex Formation

Glycyrrhizic acid belongs to amphiphilic triterpenoid saponins: its molecule comprises a hydrophobic tetracyclic aglycone and a hydrophilic disaccharide fragment with glucuronic acid residues [1–3]. In aqueous solutions, GA salts (Na_2GA, MASGA) form micelles, fibrillar aggregates, and more complex supramolecular structures with an internal hydrophobic cavity capable of incorporating nonpolar fragments of guest molecules [1,3,8,9,16]. It has been established that the stoichiometry of GA/MASGA complexes with low-molecular-weight substrates most often lies in the range of 1:1–2:1, and the stability constants KKK are in the range of 10^3–10^5 M^{-1}, which is optimal for reversible binding and solubilization [1,3,8,9,17,20,21,25,26]. For Na_2GA complexes with praziquantel and fenbendazole, characteristic spectral shifts and the transition of the drug to an amorphous state have been observed [10–13]. For MASGA, similar mechanisms have been demonstrated in complexes with cholesterol, urea, thiourea, and several pharmaceutical substances: NMR, IR spectroscopy, and thermal analysis show the formation of stable hydrogen-bonded structures with stoichiometries of 1:1–1:2, and the hydrophobic fragments of the guest molecules are shielded within the glyciram aggregates [20,21,25,26,28]. This provides a basis for efficient solubilization of hydrophobic drugs and prevents their crystallization.

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3.2. Literature Examples of MASGA Complexes and Their Biological Activity.

Studies from the domestic school (D.N. Dalimov, A.Kh. Khaitbaev, et al.) demonstrate that complexation with MASGA can significantly enhance the biological effects of substrates. Molecular complexes of ammonium glycyrrhizinate with several pharmaceutical substances, including sulfonamides, exhibit pronounced interferon-inducing activity and, in several parameters, outperform the free components [20,26].

MASGA complexes with urea, thiourea, and their derivatives improve solubility and show fungicidal and antibacterial activity against phytopathogenic microorganisms, which is associated with changes in the microenvironment and local concentrations of active substances [25,26]. The MASGA–cholesterol molecular complex, extensively studied by L.A. Yakovishin, is highly stable in water and is considered a structural platform for lipid membrane modification and potentially targeted hepatic accumulation [21]. MASGA compositions with amino acids demonstrate significant antioxidant and mitochondria-protective properties, including restoration of mitochondrial bioenergetics, reduction of lipid peroxidation levels, and normalization of respiratory parameters [17–19,28]. This opens pathways for the development of combined metabolic and cytoprotective agents. A separate set of data relates to the analytical use of MASGA as a sorbent and reagent for photometric and adsorption-spectrophotometric determination of transition metal ions (Fe^{3+}, Ni^{2+}), where reproducible complex-forming properties were demonstrated, and adsorption isotherms could be described using Langmuir and Freundlich models [22,23]. Studies on GA complexes with flavonoids (e.g., GA–quercetin) show enhanced antibacterial and antihemolytic activity against Staphylococcus aureus [27], confirming the potential of glycyrrhizinate as a platform for combined antibacterial systems.

3.3. Supramolecular MASGA Complexes with Streptocide and Sulfadimethoxine: Experimental Model

In this section, a conceptual model is proposed for experimentally investigating the ability of MASGA to function as a carrier for classic poorly soluble sulfonamides—streptocide (Str) and sulfadimethoxine (Sdz), classified as BCS Class II compounds [14]. The ranges of values presented below are design assumptions based on [11–13,17–21,25–28] and will be refined in a separate experimental study. They illustrate expected trends (solubility ranges, t_{50}/t_{90}, MIC) but do not replace results from a complete measurement cycle. All quantitative estimates should be considered as preliminary design parameters for QbD planning.

3.3.1. Experimental Objects and Design

The model substrates are pharmacopeial streptocide (Str) and sulfadimethoxine (Sdz) with purity ≥99.0 % by HPLC; the carrier is pharmacopeial MASGA [14,20,26]. Binary compositions of Str–MASGA and Sdz–MASGA are considered with molar ratios of MASGA:drug = 1:1, 2:1, 5:1, and 10:1.

For each component pair, comparisons are proposed between:

- the original drug;
- physical mixtures (PM);
- complex substances obtained via mechanochemical and solution–evaporation methods.

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All quantitative parameters in the target experimental series should be determined in a minimum of three replicates and reported as mean ± σ.

3.3.2. Preparation of Complex Substances

(Content condensed; detailed operational parameters are recommended for the Appendix.)

Mechanochemical Method: MASGA and Str/Sdz mixtures at the specified molar ratios are loaded into planetary mill capsules and ground at 300–350 rpm for up to 60 min with intermittent cooling (T ≤ 40 °C). The resulting product is sieved and stored in airtight containers. The conditions were chosen by analogy with Na_2GA complexes of praziquantel and fenbendazole [10–13]. Solution–Evaporation Method: MASGA and the respective sulfonamide are dissolved in a water:ethanol mixture (1:1) at 40 °C until a clear solution is obtained, then the solvent is removed under vacuum at T ≤ 40 °C. The resulting glassy or fine-crystalline product is ground and dried. Detailed technological parameters (milling speed, solvent characteristics, drying conditions) are recommended to be presented in the Appendix as part of the methodological section.

3.3.3. Methods of Investigation

- Stoichiometry and stability of complexes — UV titration and Higuchi–Connors diagrams; calculation of KsK_sKs using the Benesi–Hildebrand method, considering 1:1/1:2 models.
- Phase state and spectral "fingerprint" — DSC, XRPD, IR, and, where possible, NMR to confirm drug amorphization and formation of hydrogen-bonded associates.
- Equilibrium solubility and dissolution profile — saturated solution method (S, X = S/S_0) and dissolution tests (USP II, 37 °C, pH 6.8; t_{50}, t_{90}).
- Antimicrobial activity — broth microdilution method, determination of MIC against Staphylococcus aureus and Proteus mirabilis [20,26,27].

Physicochemical Characteristics of Str–MASGA and Sdz–MASGA Complexes

Based on data from related MASGA–low-molecular-weight substrate systems [1,3,17,20,21,25,26], it is expected that Str–MASGA and Sdz–MASGA will predominantly exhibit 1:1 stoichiometry, with stability constants KsK_sKs in the range of 10^4–10^5 M^{-1}. The higher hydrophobicity of Sdz justifies the assumption of a slightly higher KsK_sKs for Sdz–MASGA. It is anticipated that DSC/XRPD profiles of the complex substances will show signs of drug amorphization (disappearance of the melting endotherm, decreased intensity of crystalline peaks), and IR spectra will exhibit shifts in ν(N–H) and ν(SO_2–NH) bands, which is typical for glycyrrhizinate supramolecular systems [10–13,17–21,25–28].

Table 1. Approximate Stoichiometry and Orders of Stability Constants for Str–MASGA and Sdz–MASGA Complexes (design assumptions, UV titration, Higuchi–Connors diagrams)

System	Method	Presumed Stoichiometry	Ks, M^{-1} (order of magnitude)
Str–MACGK	UV titration, Higuchi–Connors	1:1	~10^4–10^5
Sdz–MACGK	UV titration, Higuchi–Connors	1:1	~10^4–10^5

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Note. The ranges of Ks and stoichiometry are given as approximate values based on [1,3,17,20,21,25,26]; actual values are subject to refinement in the targeted experimental series.

3.3.4. Effect of Complex Formation on Solubility and Dissolution Kinetics.

Free streptocide exhibits extremely low solubility in water (S_0(Str) on the order of 10^{-4}–10^{-3} M), whereas sulfadimethoxine is even less soluble [14]. By analogy with Na_2GK–praziquantel/fenbendazole systems and GK complexes with low-polarity acids [11–13,17–19], it is expected that the addition of submillimolar concentrations of MACGK will lead to a sharp increase in the equilibrium solubility of both sulfonamides. Approximately, the solubilization factor $X = S/S_0$ can reach 15–30 for Str and 25–60 for Sdz at [MACGK] ≈ 0.5–1.0 mM. These estimates are summarized in Table 2 as projected ranges.

Table 2. Approximate ranges of equilibrium solubility of Str and Sdz and solubilization factor X in the presence of MACGK (aqueous medium, 25 °C)

System	[MACGK], mM	S_0, M	S, M (estimate)	X = S/S_0	n
Str (free)	0	≈(1×10^{-4}–1×10^{-3})	≈S_0	1,0	—
Str–MACGK	0,5–1,0	≈(1×10^{-4}–1×10^{-3})*	≈($1{,}5\times10^{-3}$–3×10^{-2})**	15–30	—
Sdz (free)	0	qualitatively lower than S_0(Str)	≈S_0	1,0	—
Sdz–MACGK	0,5–1,0	not specified	not specified	25–60	—

Note. *S_0(Str) — estimated according to [14]. **The S range was calculated as S_0 × X and is given as an order of magnitude. All values are approximate.

For the in vitro dissolution profile (USP II, 37 °C, pH 6.8), t_{50} and t_{90} values for the free forms of Str and Sdz are expected to be "tens of minutes," with complete dissolution of Sdz potentially not achieved by 90 minutes. For the complex forms Str–MACGK and Sdz–MACGK, t_{50} decreases to approximately 5–12 min, and t_{90} to 15–30 min, corresponding to a 4–6-fold enhancement in release.

Table 3. Approximate t_{50}/t_{90} intervals and dissolution rate enhancement of Str and Sdz in the form of complexes with MACGK (USP II, 37 °C, pH 6.8)

System	Medium	t_{50}, min	t_{90}, min	Acceleration factor vs control
Str (free)	pH 6.8 (phosphate buffer)	"tens of minutes"*	"tens of minutes"*	1,0
Str–MACGK	pH 6,8	5–12	15–30	4–6
Sdz (free)	pH 6,8	"tens of minutes"*	>90 (complete dissolution not guaranteed)	1,0
Sdz–MACGK	pH 6,8	5–12	15–30	4–6

Note. *Phrasing is based on previously published dissolution curves for hydrophobic drugs in the absence of a carrier [11–13,17–19]; numerical values are subject to refinement.

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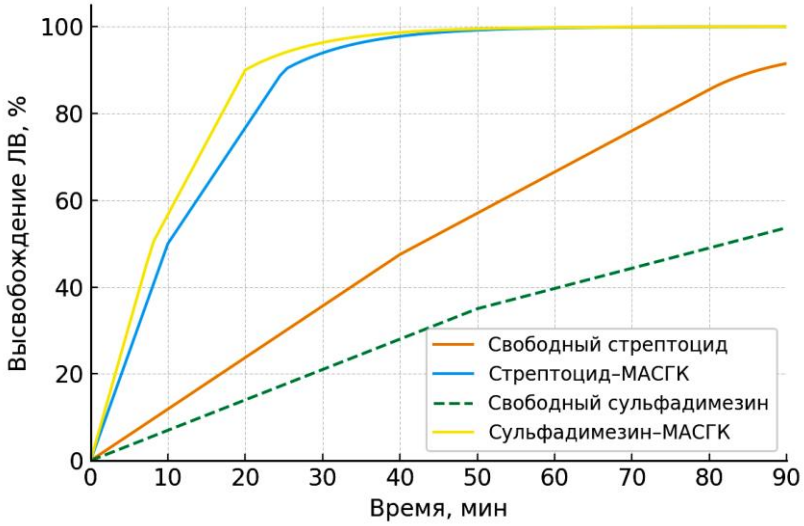

Figure 1. Generalized dissolution profiles of Str and Sdz from the free substance and supramolecular complexes with MACGK (USP II, 37 °C, pH 6.8).

On schematic dissolution curves, free Str and Sdz exhibit slow and often incomplete dissolution, whereas the complexed forms reach $t_{50} \approx 5–12$ min and $t_{90} \approx 15–30$ min. The combined effect of increased apparent solubility ($X \approx 15–30$ for Str and 25–60 for Sdz at [MASGA] ≈ 0.5–1.0 mM) and accelerated dissolution provides substantially higher concentrations of the dissolved drug over time and reduces the contribution of the dissolution step to absorption limitations for BCS Class II/IV compounds [14,29].

3.3.5. Antimicrobial Activity of Str–MASGA and Sdz–MASGA Complexes

Based on data from glycyrrhizinate complexes with drug substances [20,26,27], it can be expected that the MIC of Str and Sdz within MASGA complexes will decrease by several-fold (approximately 4–8 times) compared to the free drugs.

Table 4. Approximate Relative MIC of Str and Sdz in Free Form and as MASGA Complexes (in vitro)

System	Strain	MIC, μg/mL (free drug)	MIC, μg/mL (complex)*	Fold Reduction in MIC
Str (free)	Staphylococcus aureus	MIC_0(Str, S. aureus)	—	1,0
Str–MASGA	S. aureus	MIC_0(Str, S. aureus)	$MIC_0/4$ – $MIC_0/8$	4–8
Sdz (free)	Proteus mirabilis	MIC_0(Sdz, P. mirabilis)	—	1,0
Sdz–MASGA	P. mirabilis	MIC_0(Sdz, P. mirabilis)	$MIC_0/4$ – $MIC_0/8$	4–8

Note.* The relative ranges (expressed as MIC_0) are provided as approximate design assumptions; actual values will be determined in microbiological experiments.

A 4–8-fold reduction in MIC implies that a comparable bactericidal effect can be achieved with lower doses of the active substance, which is important from the perspectives of toxicology and resistance risk. Combined with the expected increase in exposure (AUC), analogous to Na_2GA–praziquantel systems [11–13], this provides a rationale for enhanced relative bioavailability of the complexed forms. Final confirmation requires targeted in vivo pharmacokinetic studies [11–13,17–19,27,28].

3.4. Approaches to Standardization of MASGA–Drug Complexes

Based on data from GA/MASGA systems and BCS/ICH requirements [11–14,16,29,30], a compact set of critical quality attributes (CQA) can be defined for MASGA–drug supramolecular complexes. These CQAs should form the basis of the specification and QbD approach during the development of MASGA–drug substances and corresponding pharmaceutical forms. First, complex stoichiometry must be controlled. Most GA/MASGA–guest systems exhibit ratios of 1:1 or 1:2 [1,3,8,9,17,20,21,25,26]. Stoichiometry should be confirmed not only by phase diagrams or Benesi–Hildebrand calculations, but also by independent methods (spectroscopy, DSC, XRPD). Second, the phase state of the drug is a key CQA. According to DSC and XRPD data, the final product should not contain a significant crystalline fraction of the drug. Amorphous states or finely dispersed crystalline domains are acceptable, provided that the complex dissolution profile is not inferior to that of the parent compound [10–13,26]. The third CQA block is the spectral "fingerprint**."** The complex should exhibit reproducible UV, IR, and, where possible, NMR profiles that differ from a simple physical mixture, allowing unambiguous identification of the supramolecular state [1,3,8,9,17–21]. The fourth component is the dissolution profile**.** For oral forms, an improved or at least equivalent release profile must be demonstrated. For MASGA–Str/Sdz, it is reasonable to set a criterion of t_{50}(control)/t_{50}(complex) ≥ 3–4 and to assess dissolution in at least two media (e.g., pH 1.2 and 6.8) [11–14,29]. The fifth CQA element is specific activity. Mere improvement in solubility and dissolution kinetics should be corroborated by enhanced pharmacodynamics: reduced MIC, changes in AUC and Cmax, or modifications in activity profiles. For antibacterial complexes, including MIC against test strains in the list of monitored parameters is logical [20,26,27]. Finally, reliability of routine control is essential. Regulatory documentation should specify a minimal set of routine methods (UV/IR identification, HPLC quantitative analysis, rapid dissolution test) and a separate section for extended methods (NMR, XRPD, DSC, DLS) used during development and periodic validation [11–13,20,22–24,26]. Together, stoichiometry, drug phase state, spectral profile, dissolution profile, and specific activity indicators form a coherent CQA framework for MASGA–drug complexes. This framework integrates well with the logic of ICH Q6A [29,30] and can serve as a foundation for pharmacopoeial standardization of supramolecular systems based on the monoammonium salt of glycyrrhizic acid.

3.5. Limitations and Regulatory Considerations

A key limitation for the widespread implementation of MASGA-based DDS remains the incomplete toxicological dossier for MASGA as an independent carrier. Dose-dependent adverse effects (pseudoaldosteronism, hypokalemia, arterial hypertension) and drug interactions have been described for glycyrrhizic acid and its salts [5–7]. In the transition to MASGA–drug systems, the

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safety profiles of both the drug and the carrier may change due to altered solubility, absorption, and distribution, which is critical for chronic use and parenteral or mucosal formulations.

From a regulatory perspective, MASGA–drug systems should be positioned in advance as:

- either a "special" drug substance (supramolecular complex of the API with the carrier),
- or as a combination of a "known API + new excipient."

In both scenarios, CQAs need to be formalized in accordance with ICH Q6A [29,30]: stoichiometry and phase state of the complex, dissolution profile (considering the API's BCS class [29]), spectral "fingerprint," particle size/ζ-potential for nanoformulations, and levels of impurities and free drug. The claimed advantages (increased solubility, enhanced bioavailability, reduced MIC and dosage) must be substantiated by reproducible in vitro–in vivo correlations and comparative studies with reference formulations. Recognition of MASGA as a novel excipient will require a quality control strategy (polymorphism, aggregate state, complex stability) integrated into a QbD framework (QTPP–CQA–CPP–design space), and likely early scientific-advisory discussions with regulatory authorities (EMA/FDA).

Conclusion

Supramolecular complexes based on MASGA represent a natural extension of the concept of "natural" carriers for hydrophobic drugs. A synthesis of data on GA, Na_2GA, and MASGA shows that glycyrrhizinates combine an amphiphilic structure, self-organization capability, and intrinsic pharmacological activity, making them a promising platform for the development of combined drug delivery systems (DDS) [1–3,5–7,11–13,17–21,25–28]. The model proposed in this study for MASGA–streptocide and MASGA–sulfadimethoxine complexes demonstrates a unified qualitative scenario. Complexation with the monoammonium salt of glycyrrhizic acid is expected to enhance apparent solubility, accelerate dissolution, and, consequently, increase the relative bioavailability of hydrophobic sulfonamides while maintaining or reducing the dose [11–14,17–21,27,28]. The additional contribution of the intrinsic pharmacological activity of glycyrrhizinate (anti-inflammatory, membrane-modulating, cytoprotective) provides a rationale for developing low-dose and combined formulations with a more favorable safety profile. The established set of critical quality attributes (CQA)—complex stoichiometry, phase state of the drug, spectral "fingerprint," dissolution profile, and specific activity indicators—provides a transparent framework for QbD-oriented design and standardization of MASGA–drug systems. Aligning these CQAs with ICH Q6A and BCS requirements facilitates future interactions with regulatory authorities and the preparation of regulatory documentation for MASGA–drug substances and corresponding pharmaceutical forms [11–14,20,24,26–30]. It is anticipated that, as experimental data accumulate (solubility, dissolution profiles, MIC, in vivo pharmacokinetics), supramolecular complexes of the monoammonium salt of glycyrrhizic acid will establish a stable position among platforms for delivering poorly soluble drugs. Such systems have potential applications both within conventional chemotherapeutic approaches and in the broader context of combined, personalized, and drug-repositioning strategies.

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References

1. Tolstikov GA, Murinov YuI, Baltina LA. Glycyrrhizic acid. Russ J Bioorg Chem. 1997;23(9):625–642.
2. Baltina LA. Chemical modification of glycyrrhizic acid as a route to new bioactive compounds for medicine. Curr Med Chem. 2003;10(2):155–171.
3. Graebin CS, Verli H, Barardi CRM, Simões CMO. Glycyrrhizin and glycyrrhetic acid: scaffolds to promising new pharmacologically active compounds. J Braz Chem Soc. 2010;21(9):1595–1614.
4. Hayashi H. Organ-specific production and distribution of triterpenoid saponins in Glycyrrhiza plants. Plant Biotechnol. 2009;26(1):101–106.
5. Ming LJ, Yin AC. Therapeutic effects of glycyrrhizic acid. Nat Prod Commun. 2013;8(3):415–418.
6. Zuo J, Zhang Z, Luo Q, et al. A review of the antiviral activities of glycyrrhizic acid. Pharmaceuticals. 2023;16(5):641.
7. Zhang Y, Wang J, Cao L, et al. Advances in the roles of glycyrrhizic acid in cancer therapy. Front Pharmacol. 2023;14:1265172.
8. Selyutina OYu, Polyakov NE. Glycyrrhizic acid as a multifunctional drug carrier: loading of drug molecules and targeting to lipid membranes. Int J Pharm. 2019;559:271–279.
9. Polyakov NE. Glycyrrhizic acid as a novel drug delivery vector. Open Conf Proc J. 2011;2:64–72.
10. Dushkin AV, Tolstikova TG, Murinov YuI, et al. Complexes of polysaccharides and glycyrrhizic acid with drug molecules: mechanochemical synthesis and pharmacological activity. In: Karunaratne DN, editor. The complex world of polysaccharides. Rijeka: InTech; 2012. p. 573–602.
11. Meteleva ES, Varlamova AI, Chistyachenko YuS, et al. Disodium salt of glycyrrhizic acid – a novel supramolecular delivery system for the anthelmintic drug praziquantel. J Drug Deliv Sci Technol. 2019;50:66–77.
12. Varlamova AI, Meteleva ES, Polyakov NE, et al. Biological activity of fenbendazole based on a supramolecular delivery system with disodium salt of glycyrrhizic acid. Russ J Parasitol. 2020;13(1):56–63.
13. Khalikov SS, Meteleva ES, Chistyachenko YuS, et al. Solid dispersions of anthelmintics and plant protection preparations based on disodium salt of glycyrrhizic acid. Solids. 2021;2(1):60–75.
14. Song J, Sun H, Wang Y, et al. Formulation of glycyrrhizic acid-based nanocomplexes for tumor-targeted drug delivery. Biotechnol Bioprocess Eng. 2022;27:163–174.
15. Yu X, Zhang X, Liu Y, et al. Tunable glycyrrhizic acid supramolecular hydrogels via metal ions for biomedical applications. Mater Today Bio. 2024;22:100793.
16. Zhao ZW, Zhao L, Wang Y, et al. Application of glycyrrhizic acid and glycyrrhetinic acid in the drug delivery system. J Drug Deliv Sci Technol. 2023;78:104019.
17. Babaeva DT, Sharafutdinov MR, Gabbasov TM, et al. Biological activity of the supramolecular complex of glycyrrhizic and salicylic acids. Chem Nat Compd. 2020;56(2):278–281.

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18. Lolakhon E, Mamirqulova GT, et al. Acquisition of supramolecular complex of glycyrrhizic acid with menthol and their chemical identification. Universum Chem Biol. 2020. Russian.
19. Ettibaeva LA, Abdurahmonova UK, Matchanov AD, Karshiboev S. Effects of glycyrrhizinic acid, menthol and GA:Mt (2:1), GA:Mt (4:1) and GA:Mt (9:1) supramolecular compounds on mitochondrial functional activity in vitro experiments. J Integr Nat Sci. 2022;15(4):137–144.
20. Dalimov DN, Isaev YuT, Saiitkulov AM. Molecular complexes of ammonium glycyrrhizate with certain medicinal agents and their interferon-inducing activity. Chem Nat Compd. 2001;37(2):151–153.
21. Yakovishin LA. Molecular complex of glycyrrhizic acid monoammonium salt with cholesterol. Curr Bioact Compd. 2020;16(7):1042–1048.
22. Abdurahmanova KU, Kushiev KH, Iroda MJ. Adsorption properties of monoammonium salt of glycyrrhizic acid. Int J Curr Microbiol Appl Sci. 2021;10(4):823–829.
23. Abdurakhmanova UK, Kushiev KH. Sorption-spectrometric determination of nickel by monoammonium salt of glycyrrhizic acid. Chem Chem Eng. 2021;1:12–18.
24. Khaitbaev AKh, Toshov KhS, Nazirova YaK. Development of quality control methods and standardization of the megaferron substance. Eurasian Union of Scientists. 2020;1(70):56–62. Russian. doi:10.31618/ESU.2413-9335.2020.3.70.543
25. Askarov IR, Saiitkulov AM, Isaev YuT, et al. Synthesis of complex compounds of monoammonium salt of glycyrrhizic acid and thiourea. E3S Web Conf. 2023;383:04023.
26. Dalimov DN, Toshov KhS, Khaitbaev AKh. Synthesis, composition and some physical and chemical properties of supramolecular complexes of glycyrrhizic acid. Uzbek Chem J. 2018;6:3–10.
27. Olchowik-Grabarek E, Czerwonka A, Komosa A, et al. Antibacterial and antihemolytic activity of new biomaterial based on glycyrrhizic acid and quercetin against Staphylococcus aureus. J Funct Biomater. 2023;14(7):368.
28. Esanov R, et al. Study of antioxidant properties and influence on mitochondrial bioenergetics of a composition consisting of monoammonium salt of glycyrrhizic acid and amino acids. J Neonatal Surg. 2025;14(7S):141–147.
29. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413–420.
30. International Conference on Harmonisation (ICH). ICH harmonised tripartite guideline Q6A: Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances. Geneva: ICH; 1999.

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