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EP 1341556 B1
Chemical Communications, 2001, pages 2342-2343
Journal of Scientific & Industrial Research, 2009, pages 267-272
Journal of Colloid and Interface Science, vol. 356, 2011, pages 566-572
Journal of Hazardous Materials, vol. 185, No. 2-3, 2011, pages 1435-1439
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Applied Clay Science, vol. 109-110, 2015, pages 119-126
Journal of Dispersion Science and Technology, vol. 33, No. 1-3, pages 339-345
International Journal of Nanomedicine, vol. 9, 2014, pages 4867-4878 [available via https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4211912/]

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Other: **CAS ONLINE, EPODOC, WPI, MEDLINE, BIOSIS**
updated as appropriate

Additional Fields
Other: **None**

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GB 2555442 B

FIGURE 1

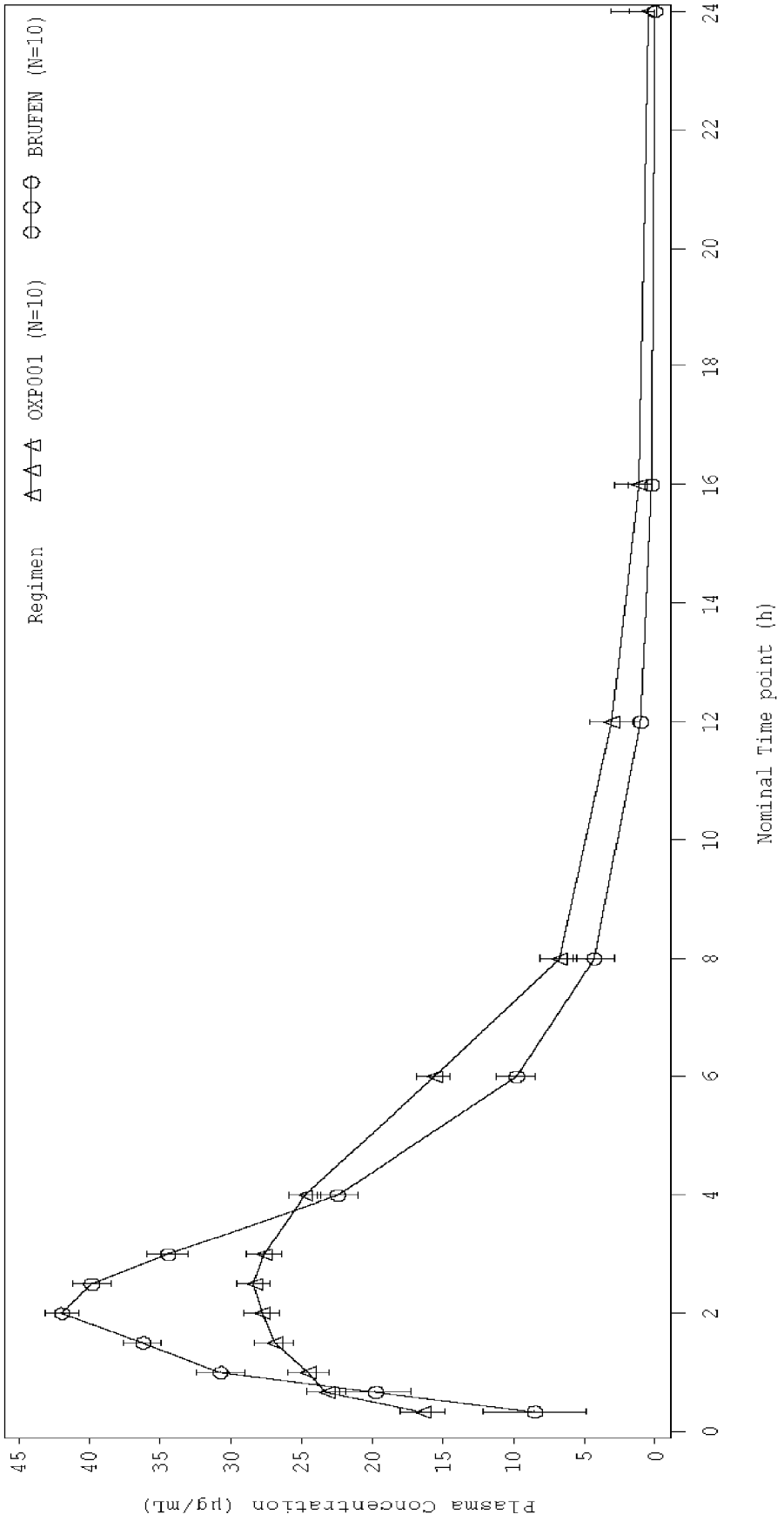
Regimen Δ Δ Δ OXP001 (N=10) ○ ○ ○ BRUFEN (N=10)
Plasma Concentration (µg/mL)
Nominal Time point (h)
0
5
10
15
20
25
30
35
40
45
0
2
4
6
8
10
12
14
16
18
20
22
24

FIGURE 2

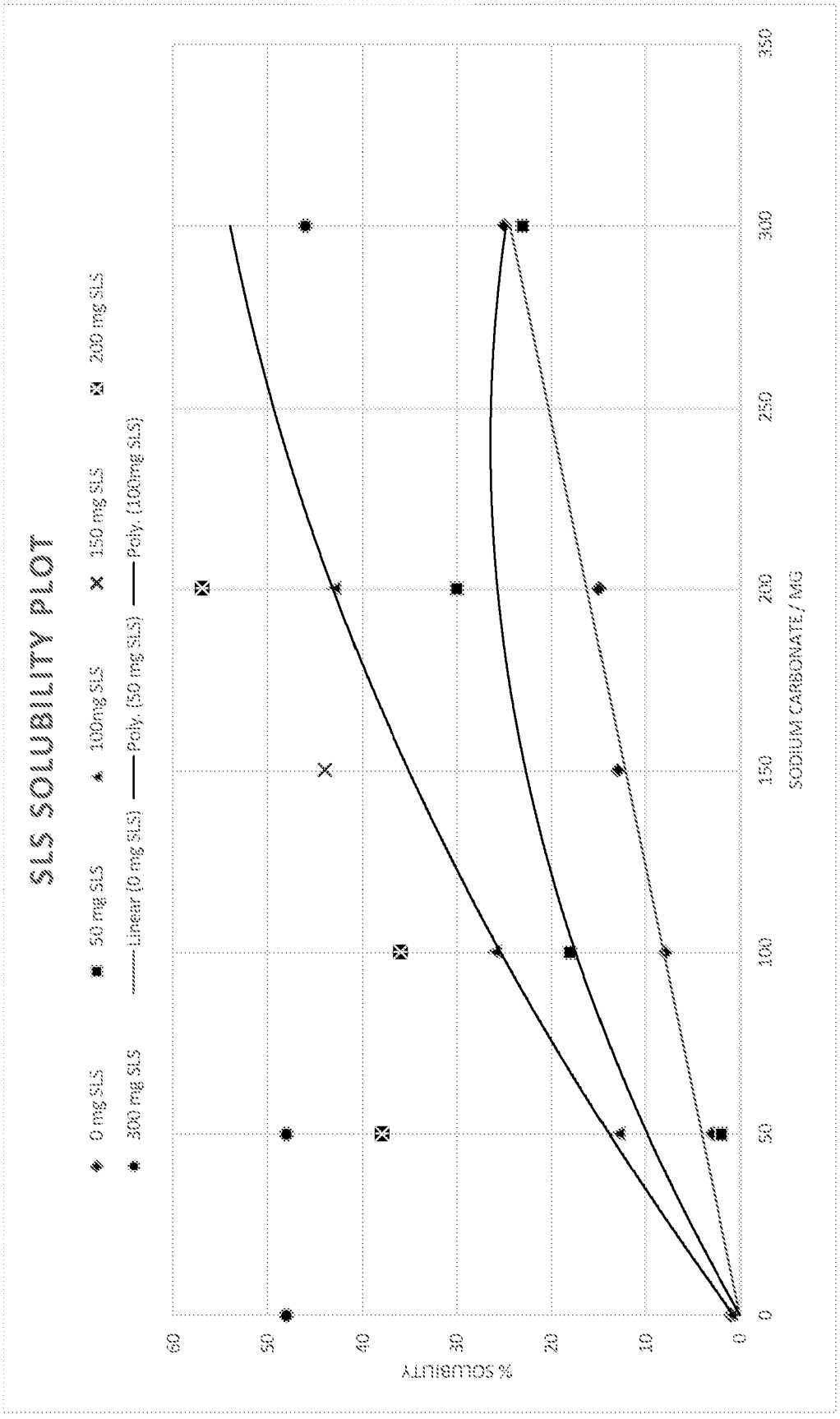
SLS SOLUBILITY PLOT
0 mg SLS
50 mg SLS
100mg SLS
150 mg SLS
200 mg SLS
300 mg SLS
Linear (0 mg SLS)
Poly. (50 mg SLS)
Poly. (100mg SLS)
% SOLUBILITY
SODIUM CARBONATE / MG
0
10
20
30
40
50
60
0
50
100
150
200
250
300
350

FIGURE 3

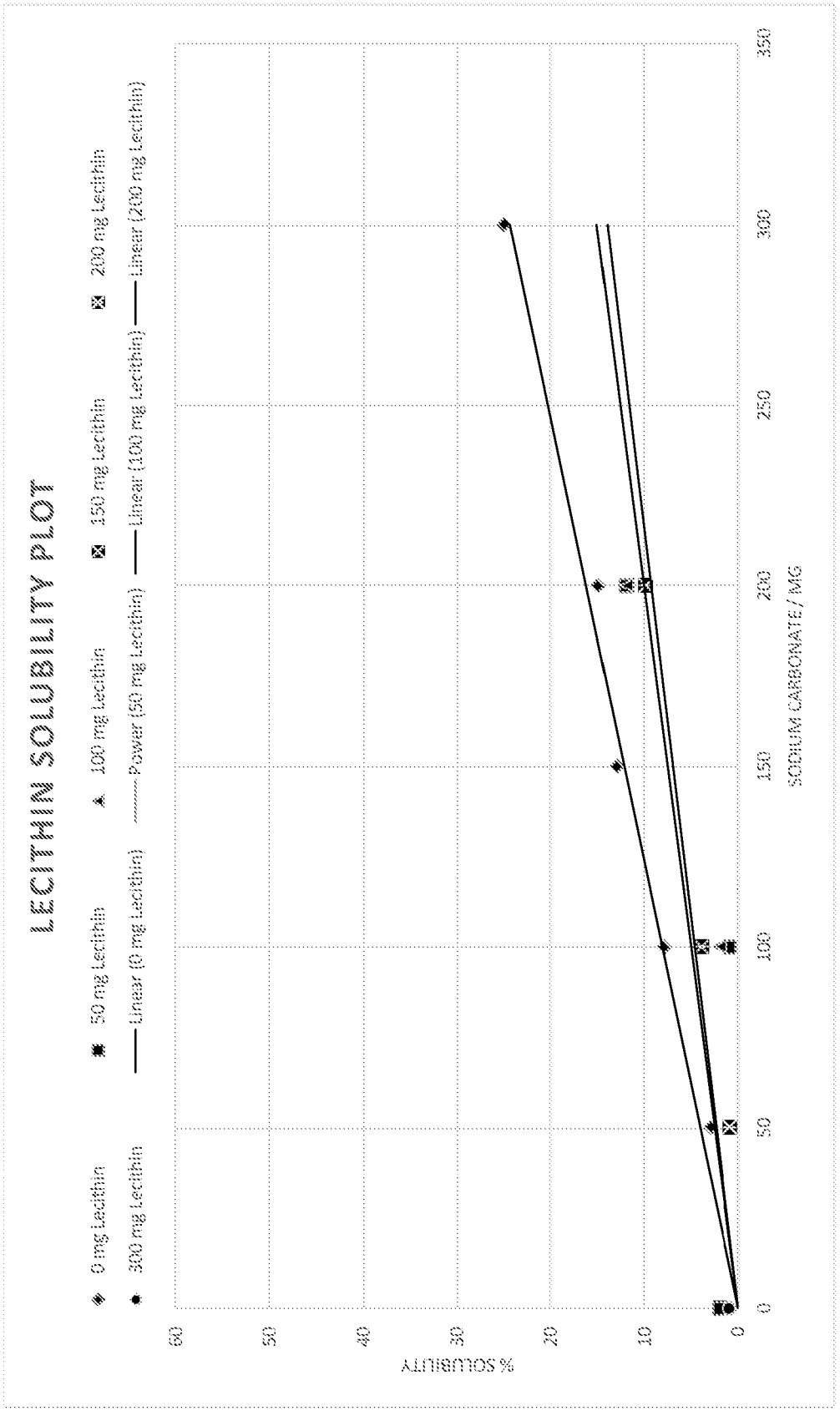
LECITHIN SOLUBILITY PLOT
0 mg Lecithin
50 mg Lecithin
100 mg Lecithin
150 mg Lecithin
200 mg Lecithin
300 mg Lecithin
Linear (0 mg Lecithin)
Power (50 mg Lecithin)
Linear (100 mg Lecithin)
Linear (200 mg Lecithin)
% SOLUBILITY
SODIUM CARBONATE / MG
0
10
20
30
40
50
60
0
50
100
150
200
250
300
350

FIGURE 4

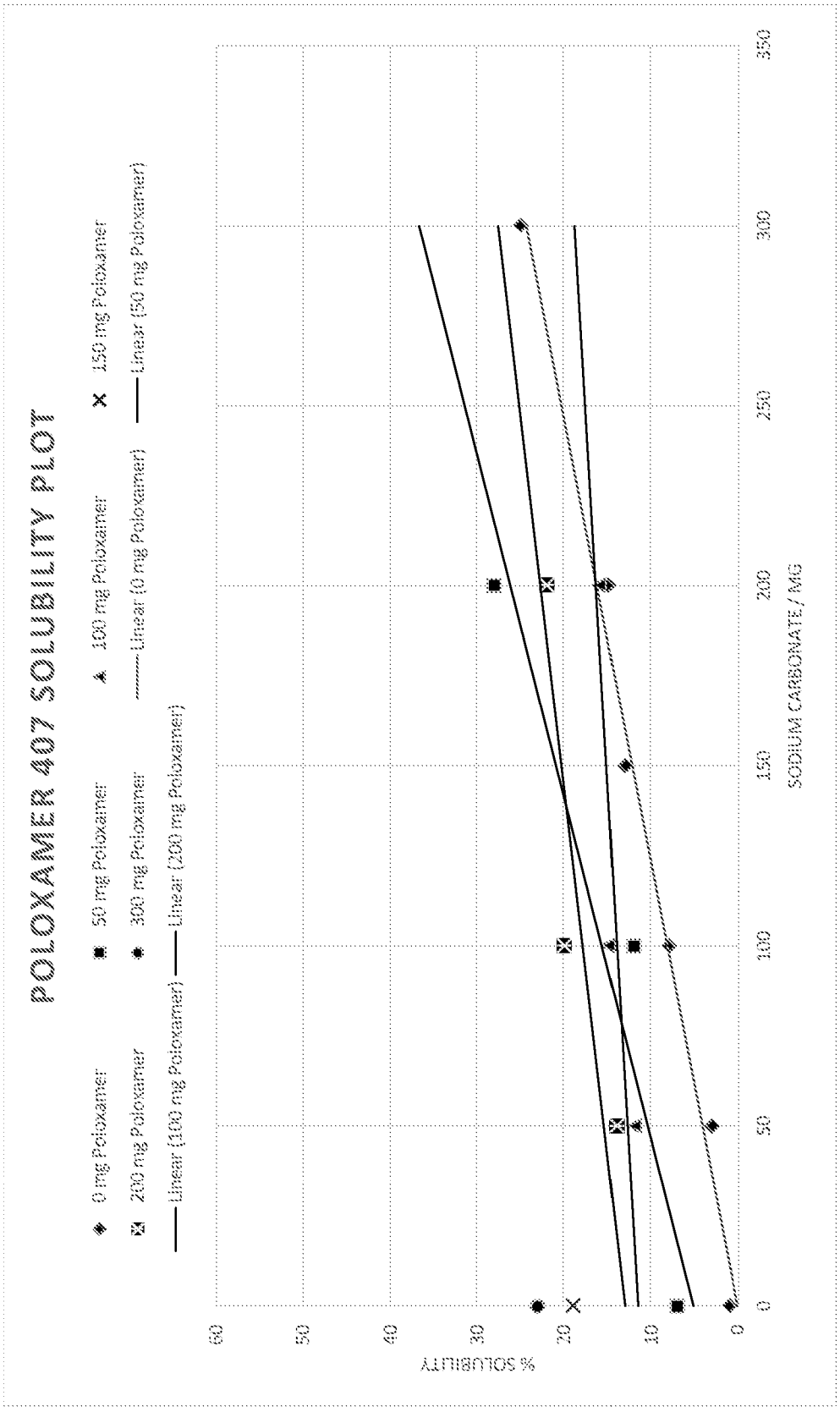
POLOXAMER 407 SOLUBILITY PLOT
0 mg Poloxamer
50 mg Poloxamer
100 mg Poloxamer
150 mg Poloxamer
200 mg Poloxamer
300 mg Poloxamer
Linear (0 mg Poloxamer)
Linear (50 mg Poloxamer)
Linear (100 mg Poloxamer)
Linear (200 mg Poloxamer)
% SOLUBILITY
SODIUM CARBONATE / MG
0
10
20
30
40
50
60
0
50
100
150
200
250
300
350

FIGURE 5

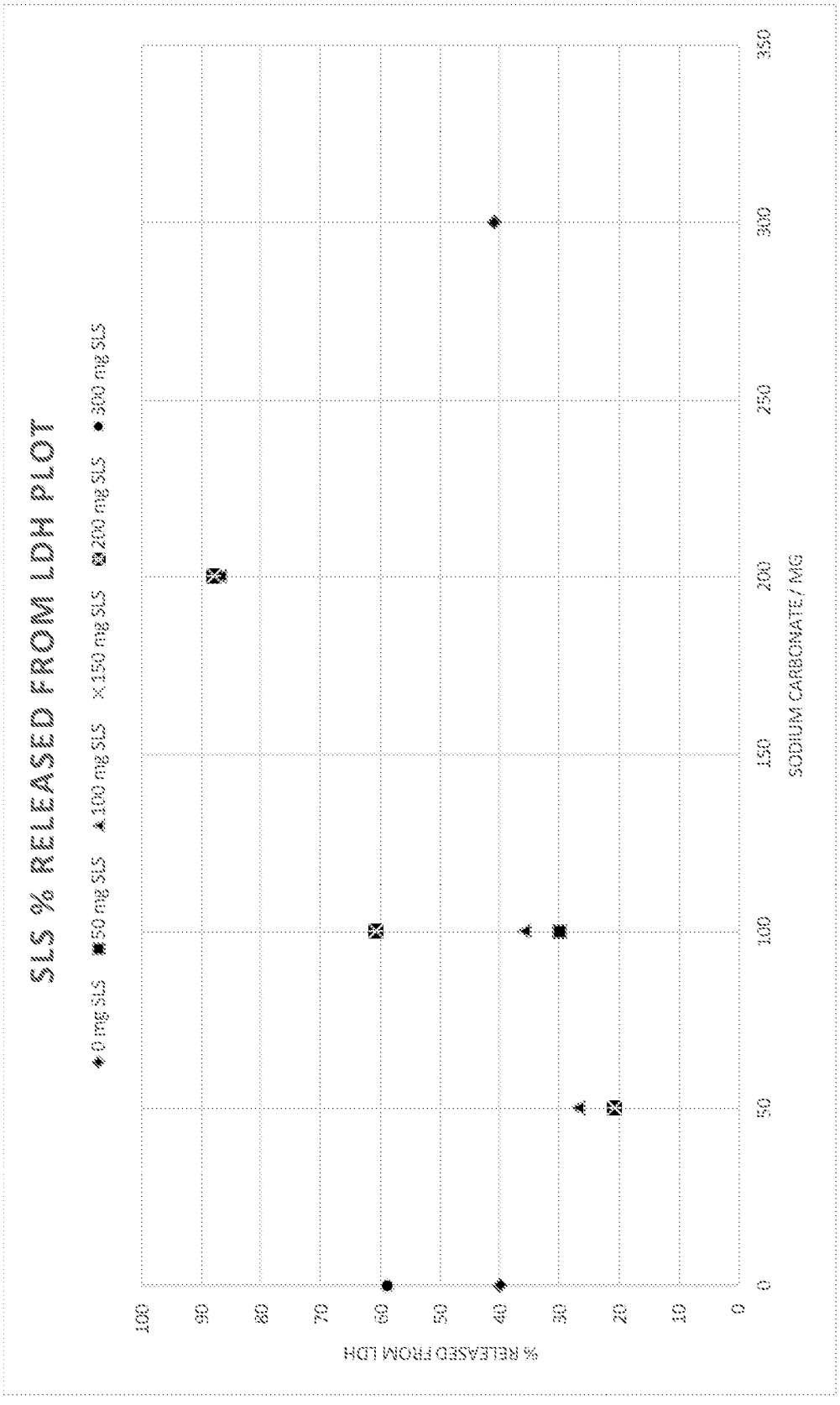
SLS % RELEASED FROM LDH PLOT
0 mg SLS
50 mg SLS
100 mg SLS
150 mg SLS
200 mg SLS
300 mg SLS
% RELEASED FROM LDH
SODIUM CARBONATE / MG
0
10
20
30
40
50
60
70
80
90
100
0
50
100
150
200
250
300
350

FIGURE 6

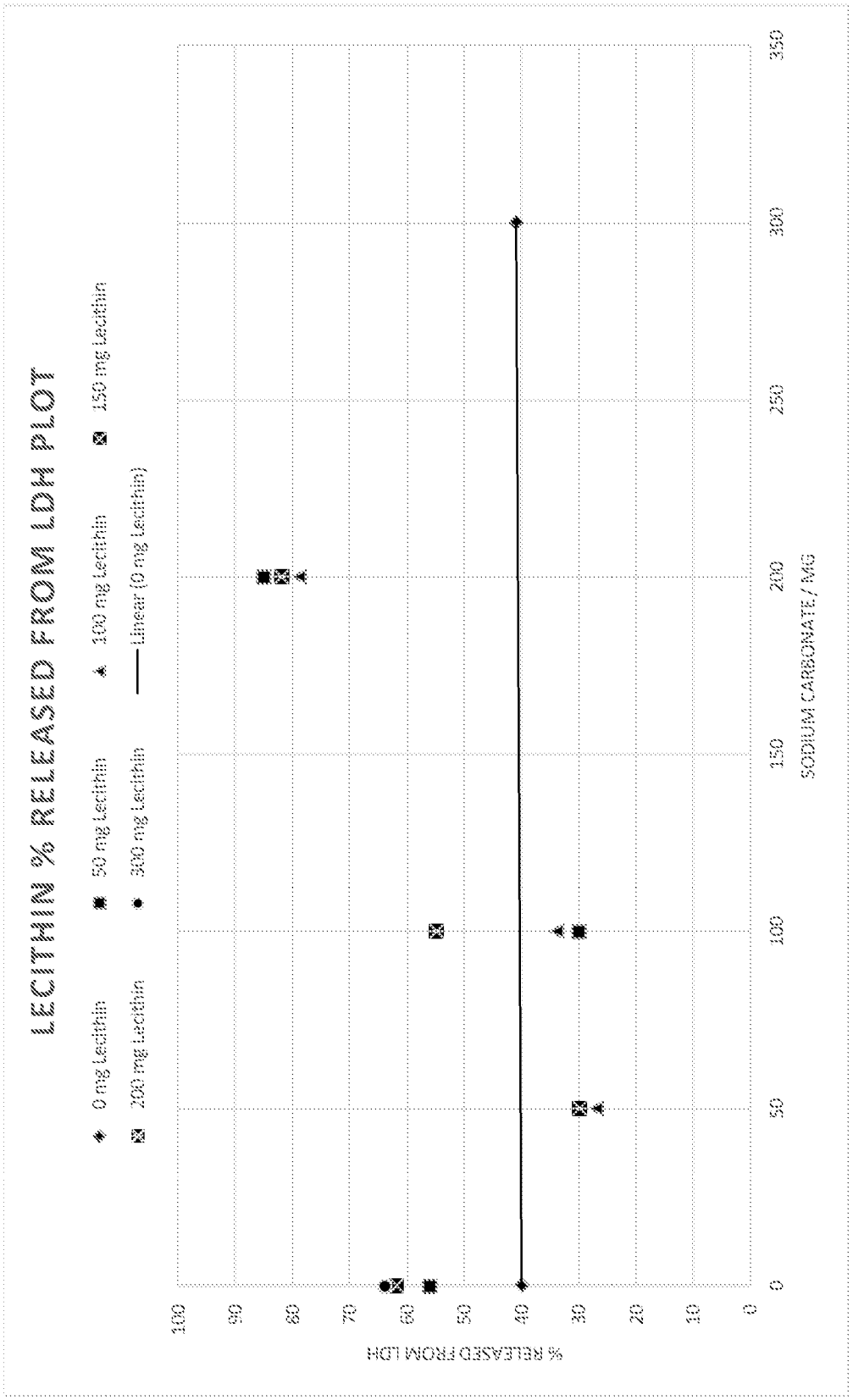
LECITHIN % RELEASED FROM LDH PLOT
0 mg Lecithin
50 mg Lecithin
100 mg Lecithin
150 mg Lecithin
200 mg Lecithin
300 mg Lecithin
Linear (0 mg Lecithin)
% RELEASED FROM LDH
SODIUM CARBONATE / MG
0
10
20
30
40
50
60
70
80
90
100
0
50
100
150
200
250
300
350

FIGURE 7

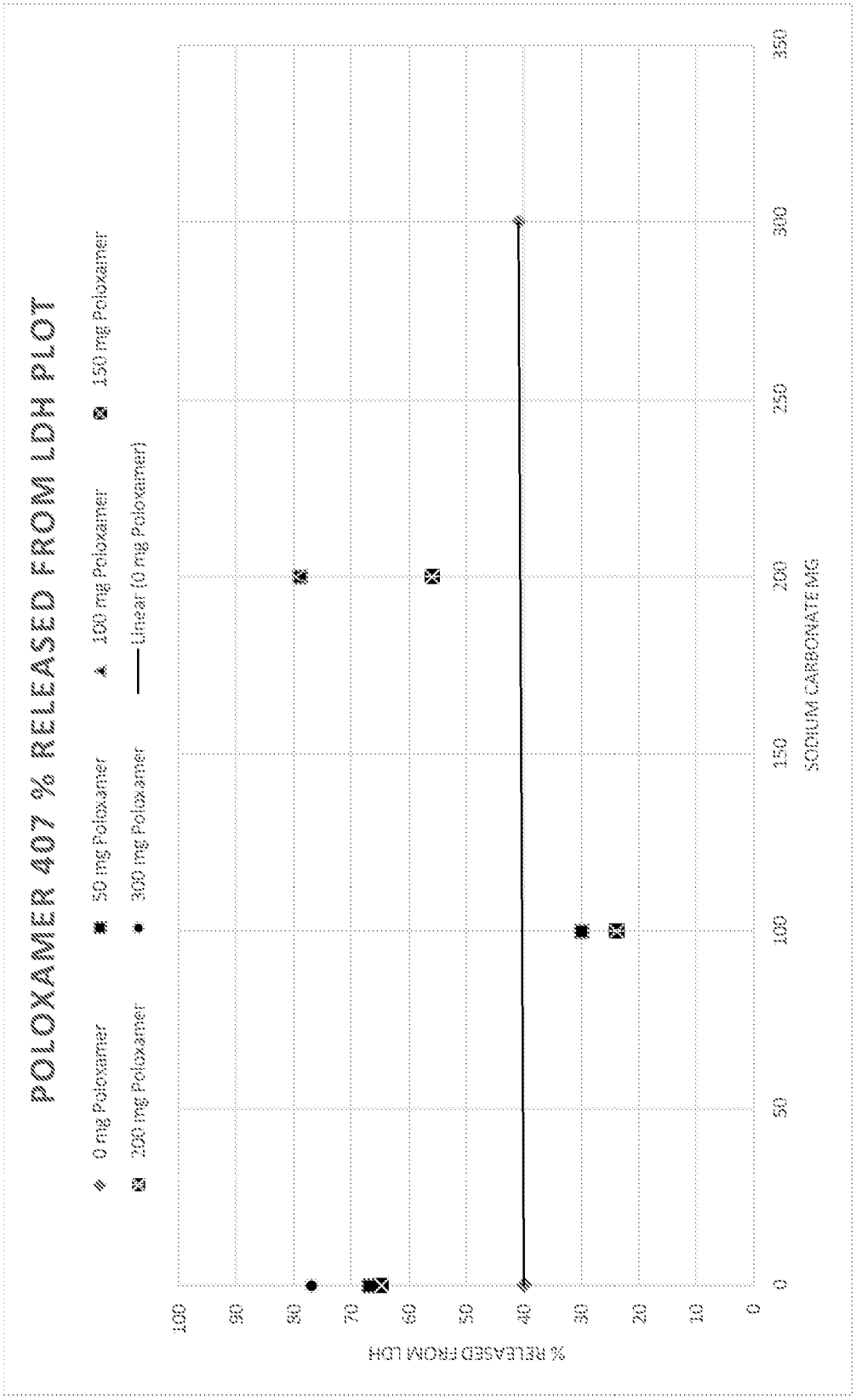
POLOXAMER 407 % RELEASED FROM LDH PLOT
0 mg Poloxamer
50 mg Poloxamer
100 mg Poloxamer
150 mg Poloxamer
200 mg Poloxamer
300 mg Poloxamer
Linear (0 mg Poloxamer)
% RELEASED FROM LDH
SODIUM CARBONATE MG
0
10
20
30
40
50
60
70
80
90
100
0
50
100
150
200
250
300
350

FIGURE 8

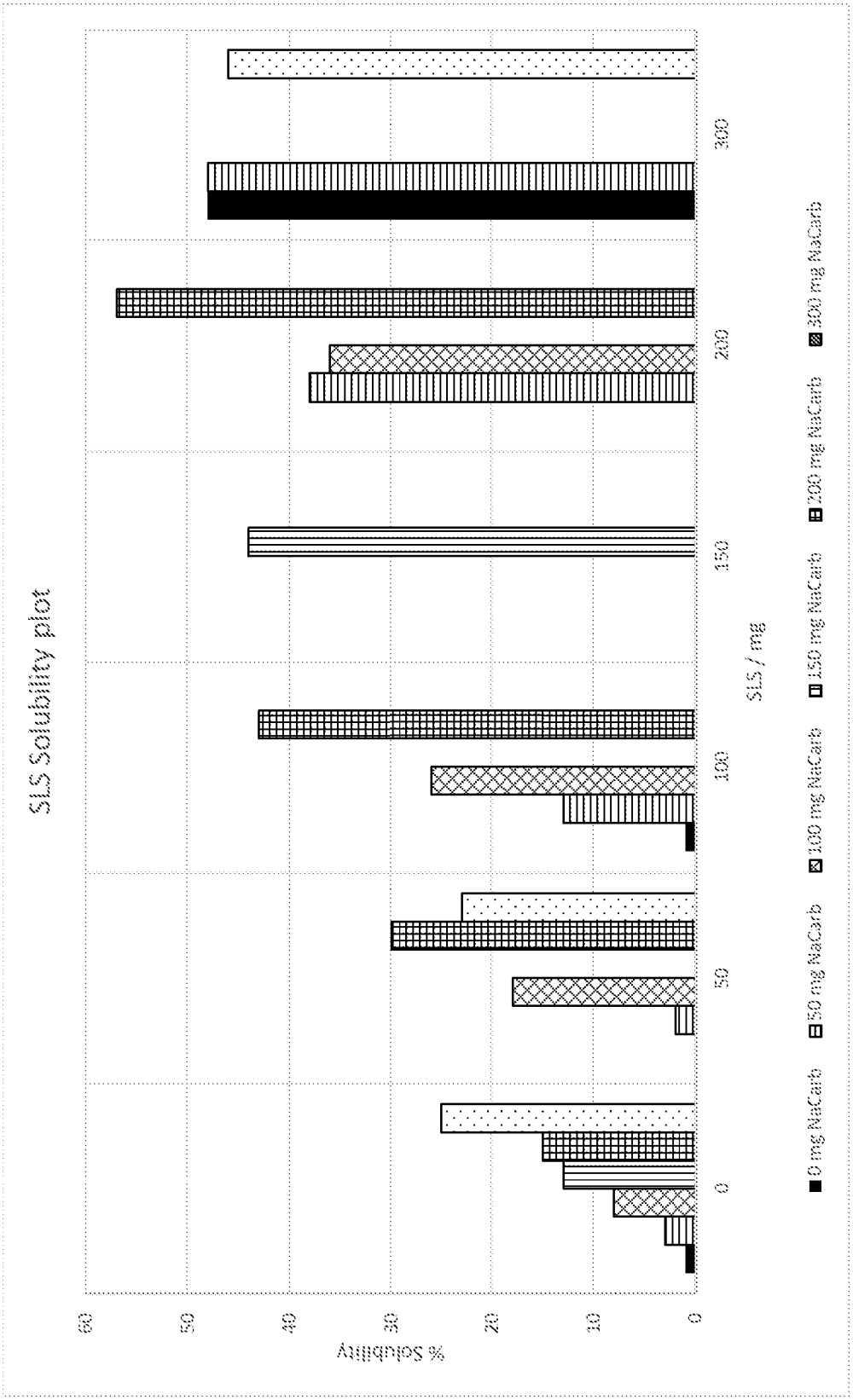
SLS Solubility plot
% Solubility
0
10
20
30
40
50
60
SLS / mg
0
50
100
150
200
300
0 mg NaCarb
50 mg NaCarb
100 mg NaCarb
150 mg NaCarb
200 mg NaCarb
300 mg NaCarb

FIGURE 9

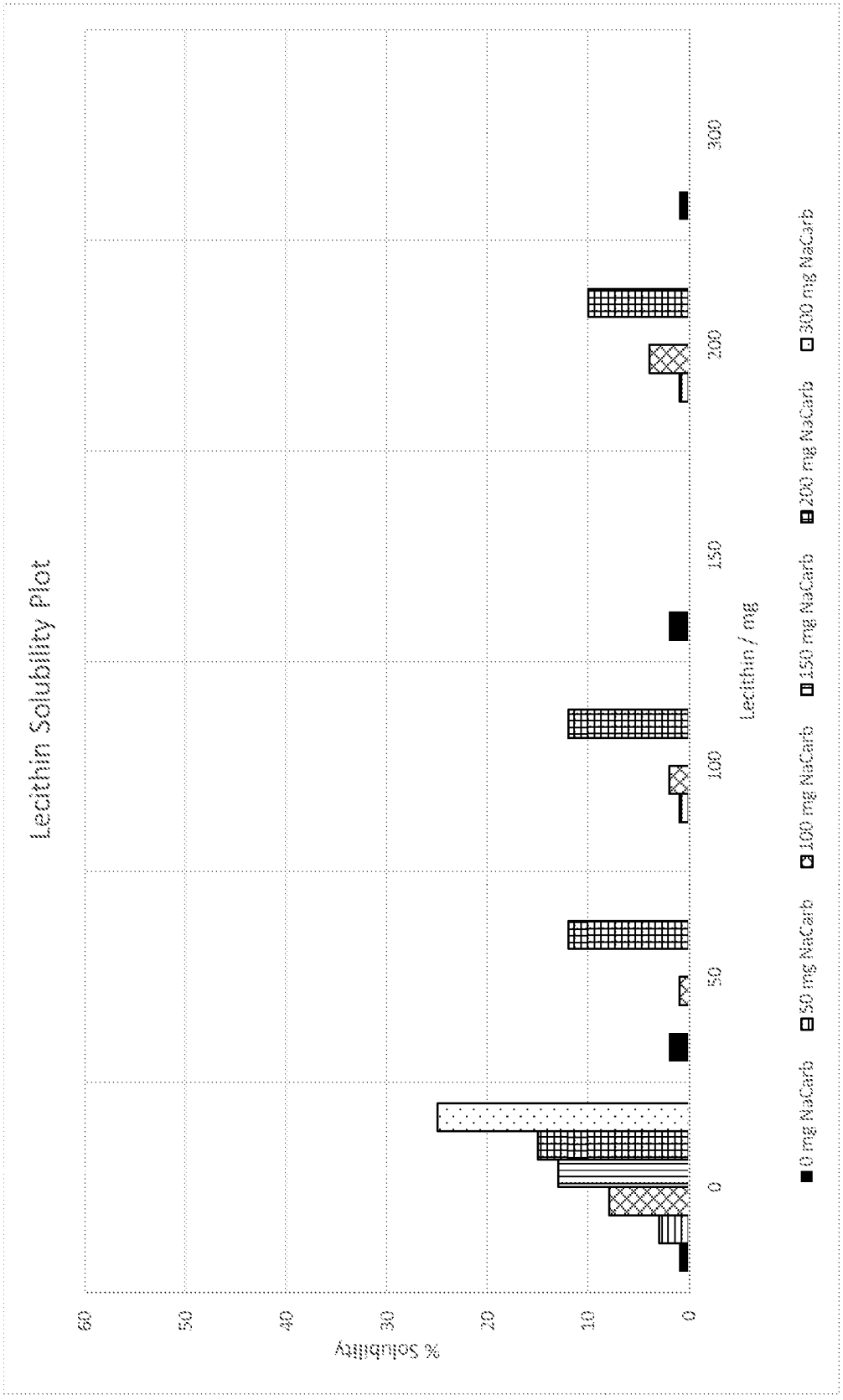
Lecithin Solubility Plot
% Solubility
0
10
20
30
40
50
60
0
50
100
150
200
300
Lecithin / mg
0 mg NaCarb
50 mg NaCarb
100 mg NaCarb
150 mg NaCarb
200 mg NaCarb
300 mg NaCarb

FIGURE 10

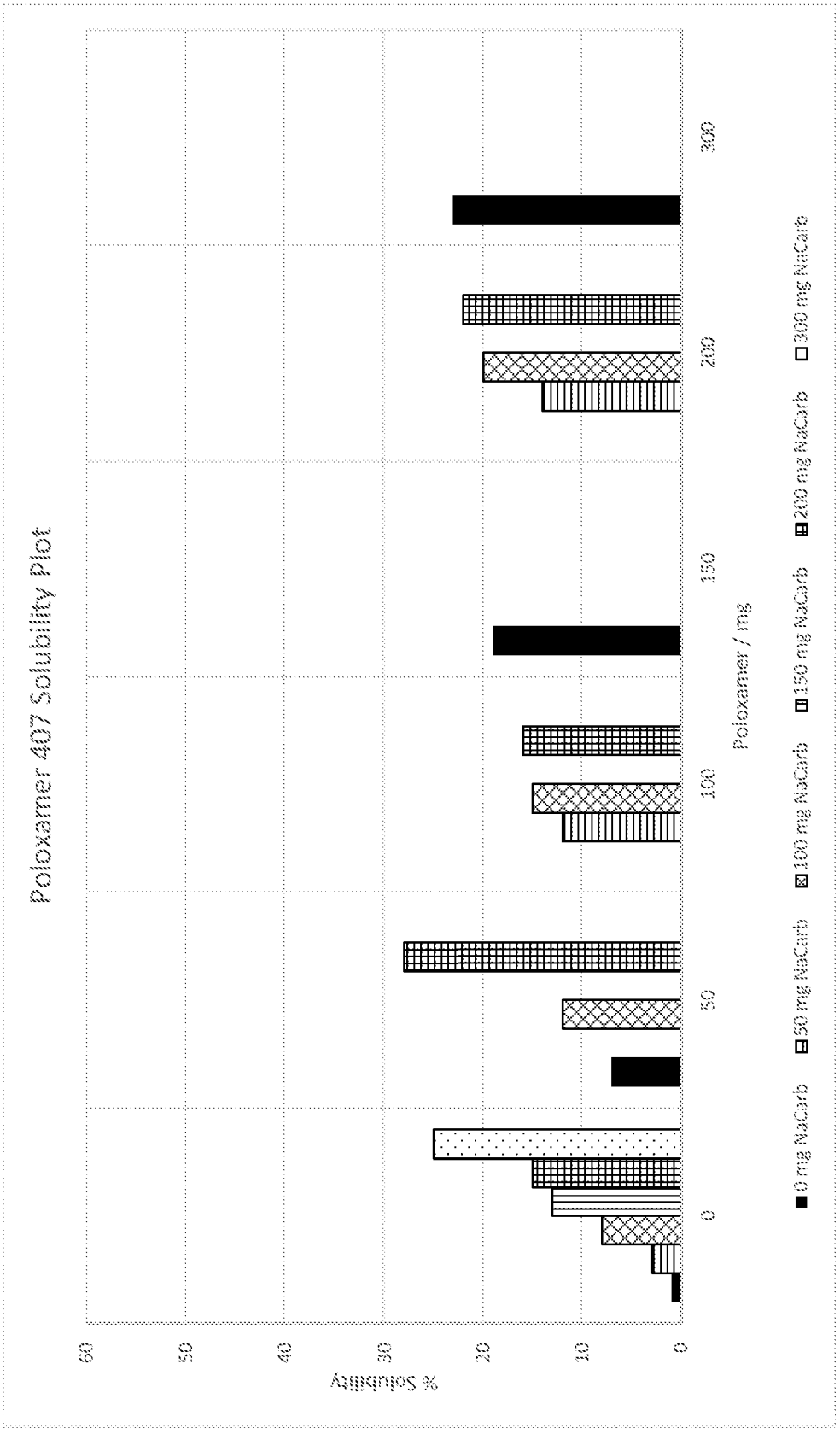
Poloxamer 407 Solubility Plot
% Solubility
0
10
20
30
40
50
60
0
50
100
150
200
300
Poloxamer / mg
0 mg NaCarb
50 mg NaCarb
100 mg NaCarb
150 mg NaCarb
200 mg NaCarb
300 mg NaCarb

FIGURE 11

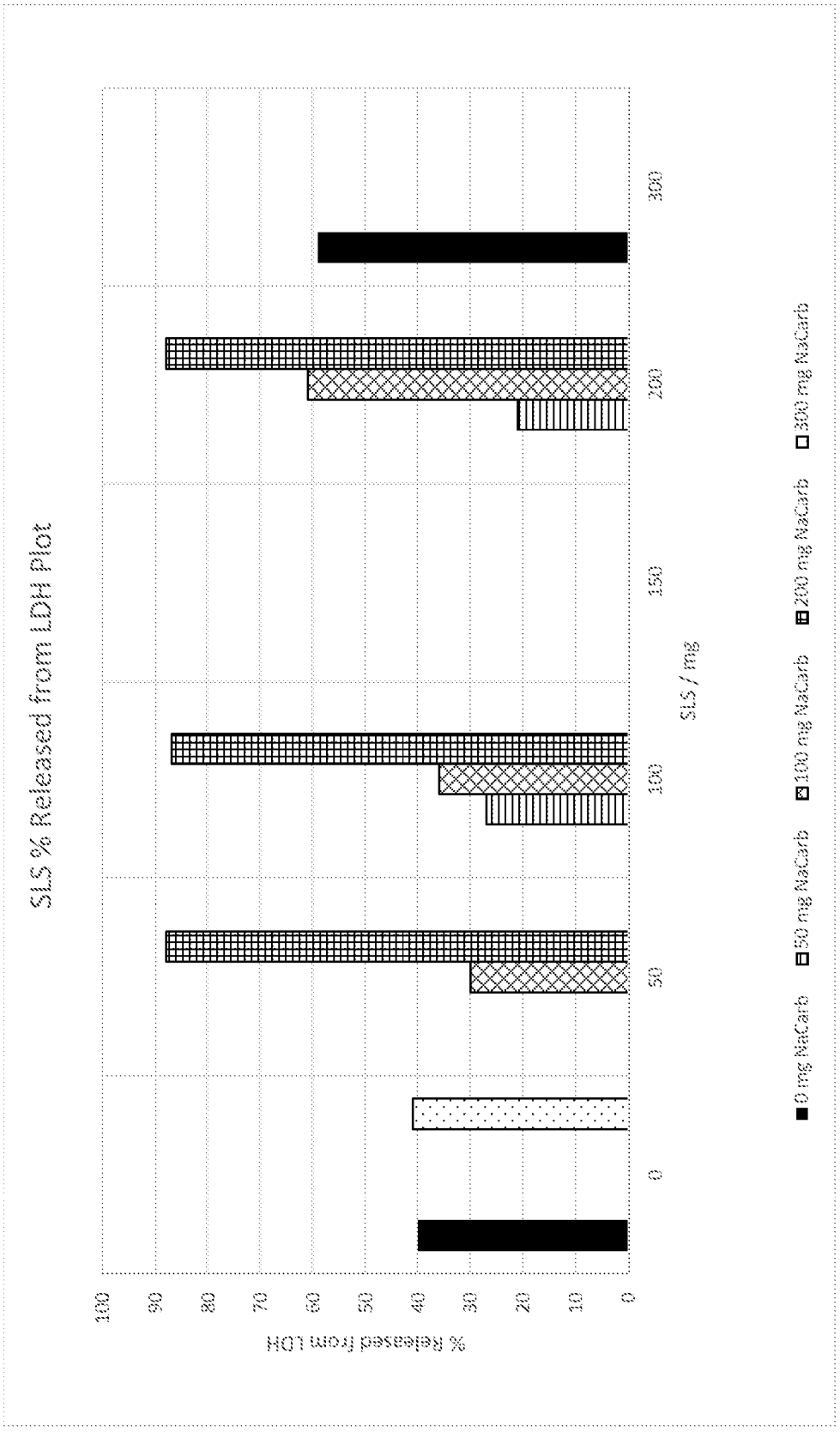
SLS % Released from LDH Plot
% Released from LDH
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
300
SLS / mg
0 mg NaCarb
50 mg NaCarb
100 mg NaCarb
200 mg NaCarb
300 mg NaCarb

FIGURE 12

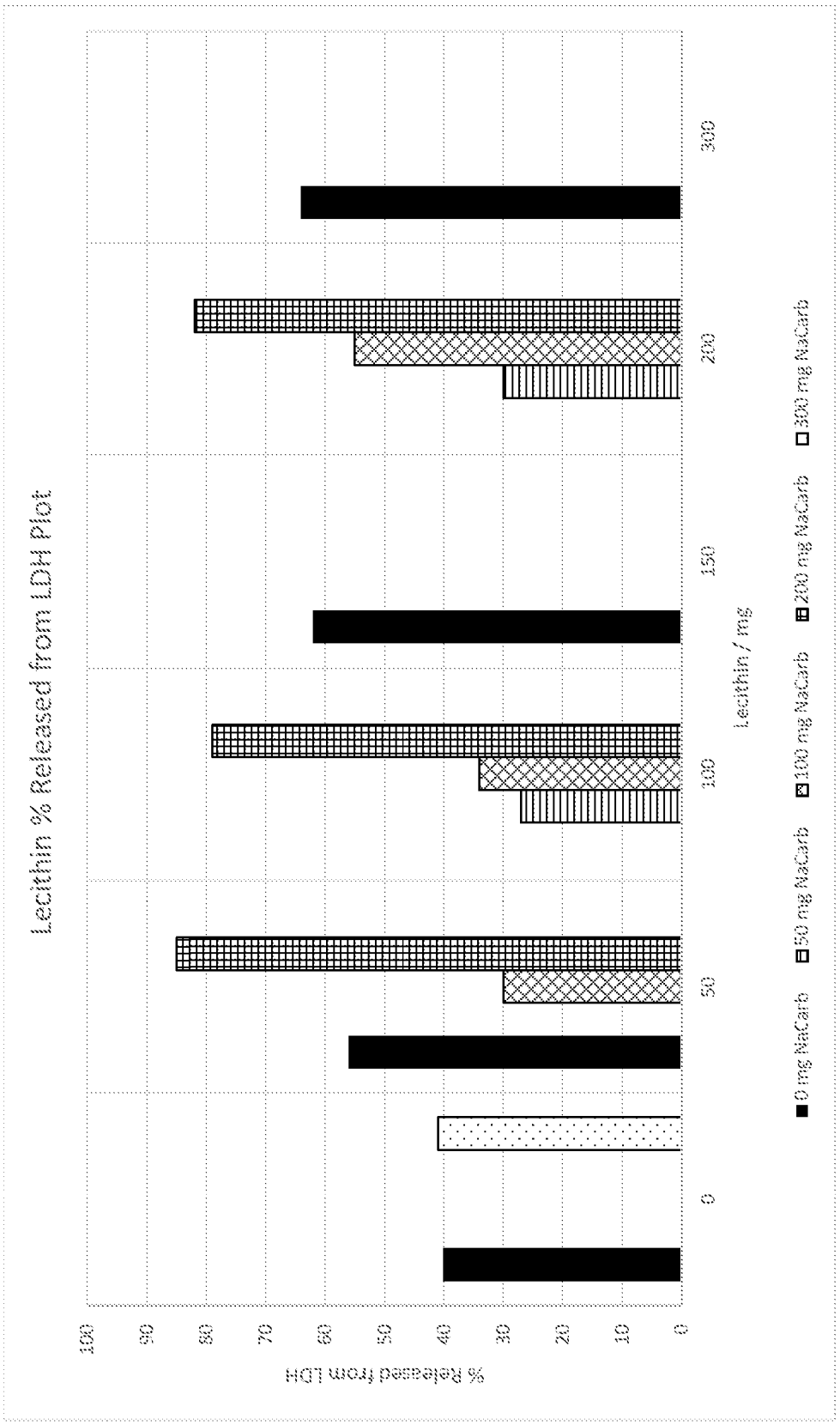
Lecithin % Released from LDH Plot
% Released from LDH
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
300
Lecithin / mg
0 mg NaCarb
50 mg NaCarb
100 mg NaCarb
200 mg NaCarb
300 mg NaCarb

FIGURE 13

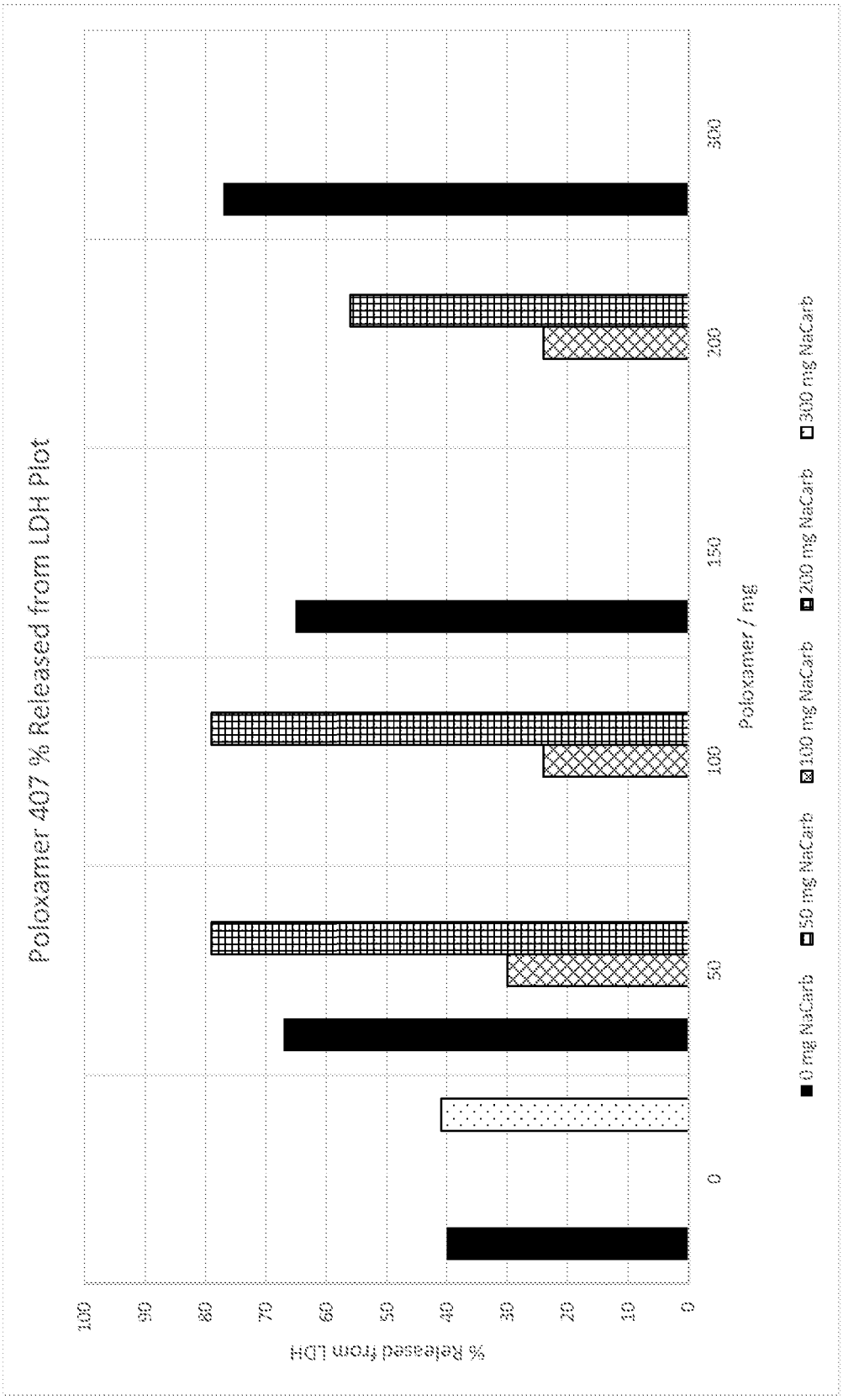
Poloxamer 407 % Released from LDH Plot
% Released from LDH
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
300
Poloxamer / mg
0 mg NaCarb
50 mg NaCarb
100 mg NaCarb
200 mg NaCarb
300 mg NaCarb

FIGURE 14

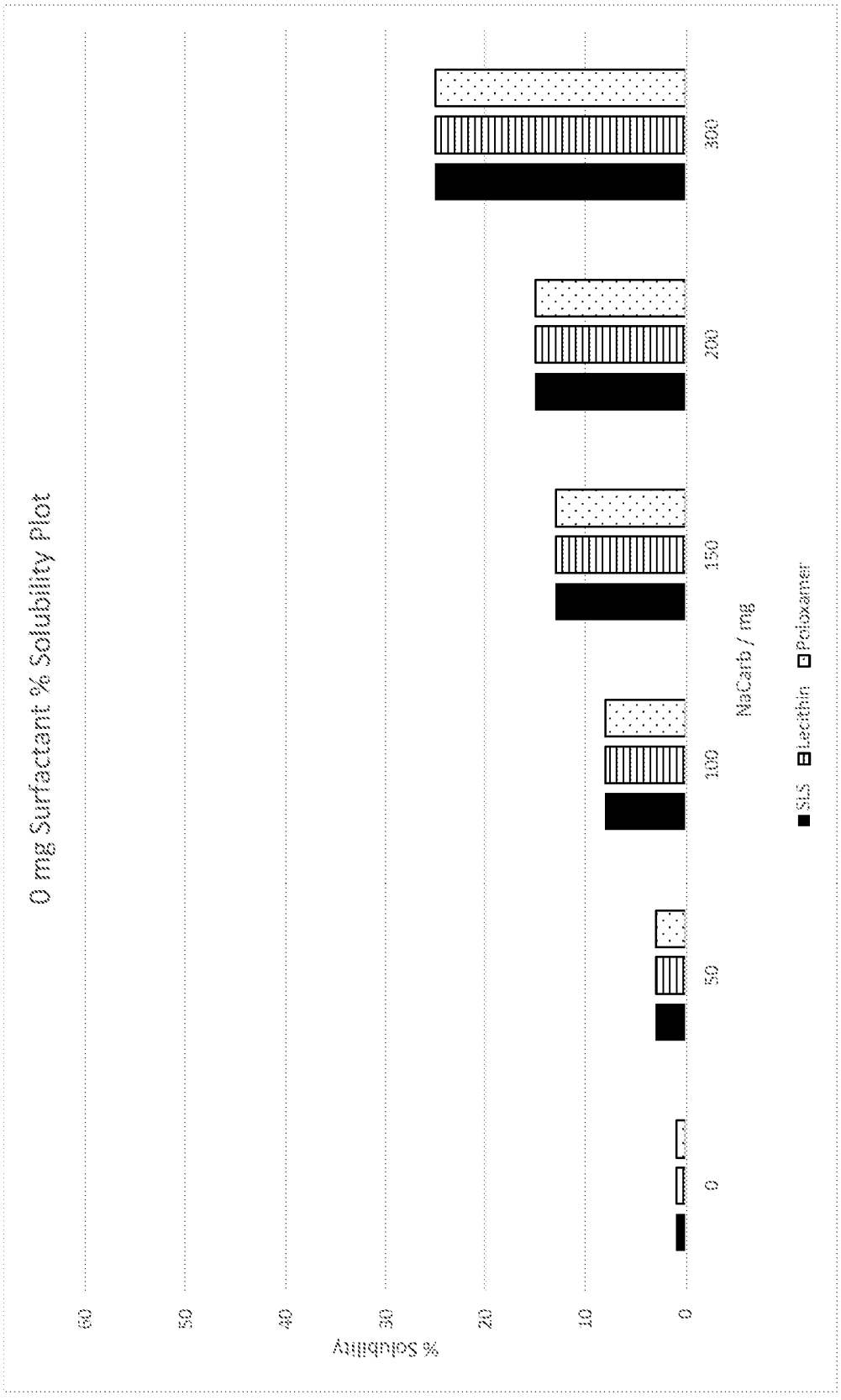
0 mg Surfactant % Solubility Plot
% Solubility
0
10
20
30
40
50
60
0
50
100
150
200
300
NaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 15

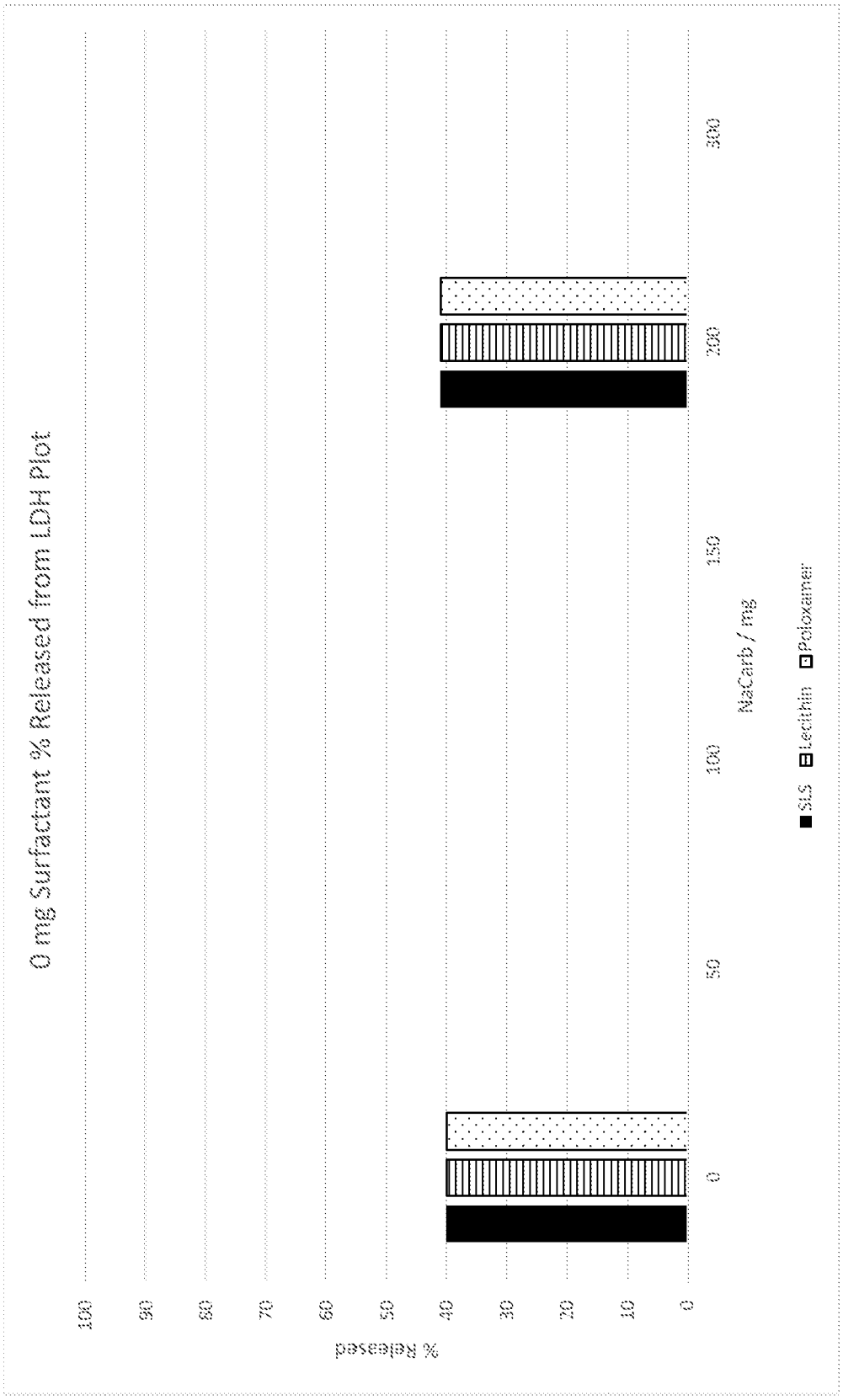
0 mg Surfactant % Released from LDH Plot
% Released
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
300
NaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 16

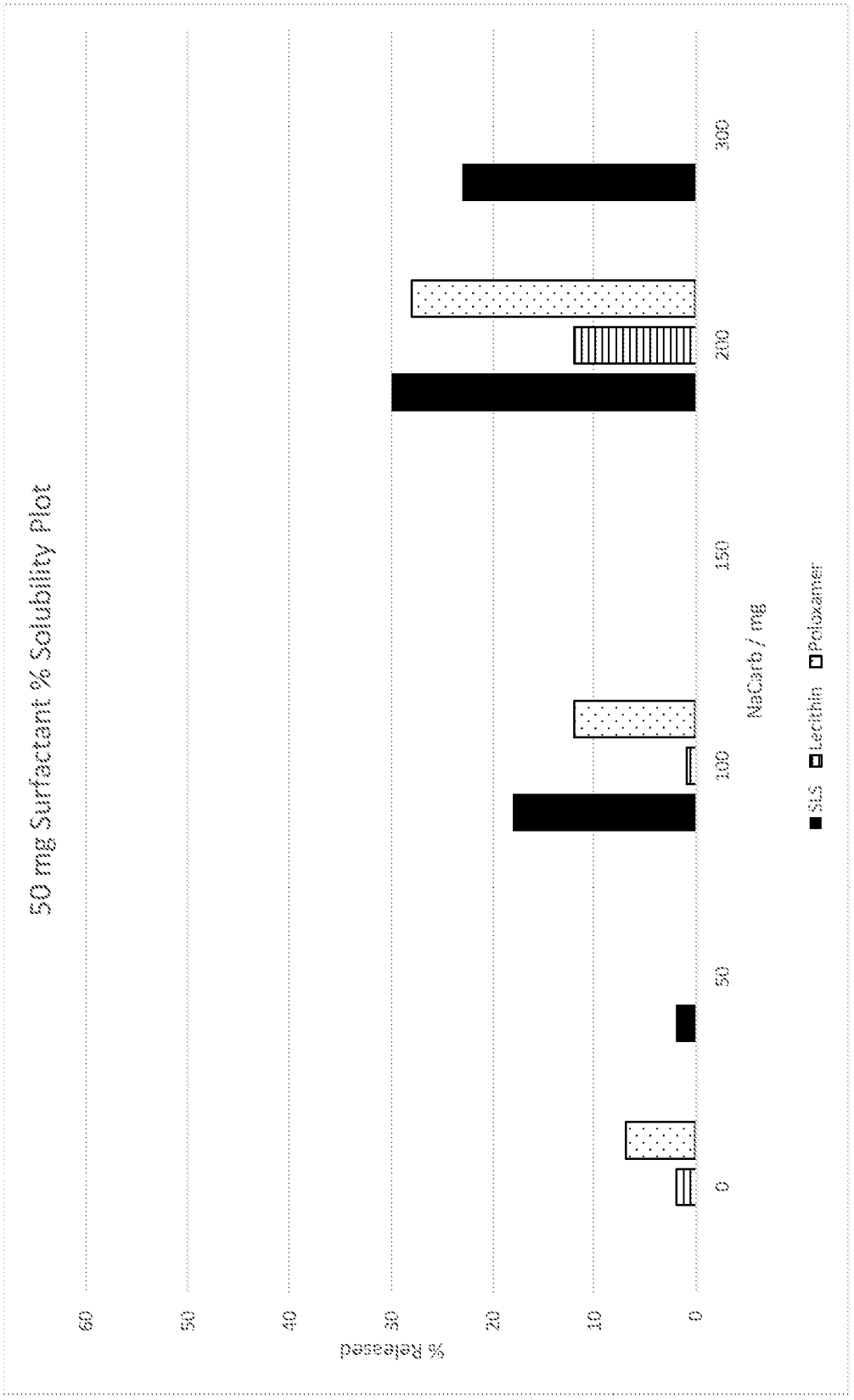
50 mg Surfactant % Solubility Plot
% Released
0
10
20
30
40
50
60
0
50
100
150
200
300
NaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 17

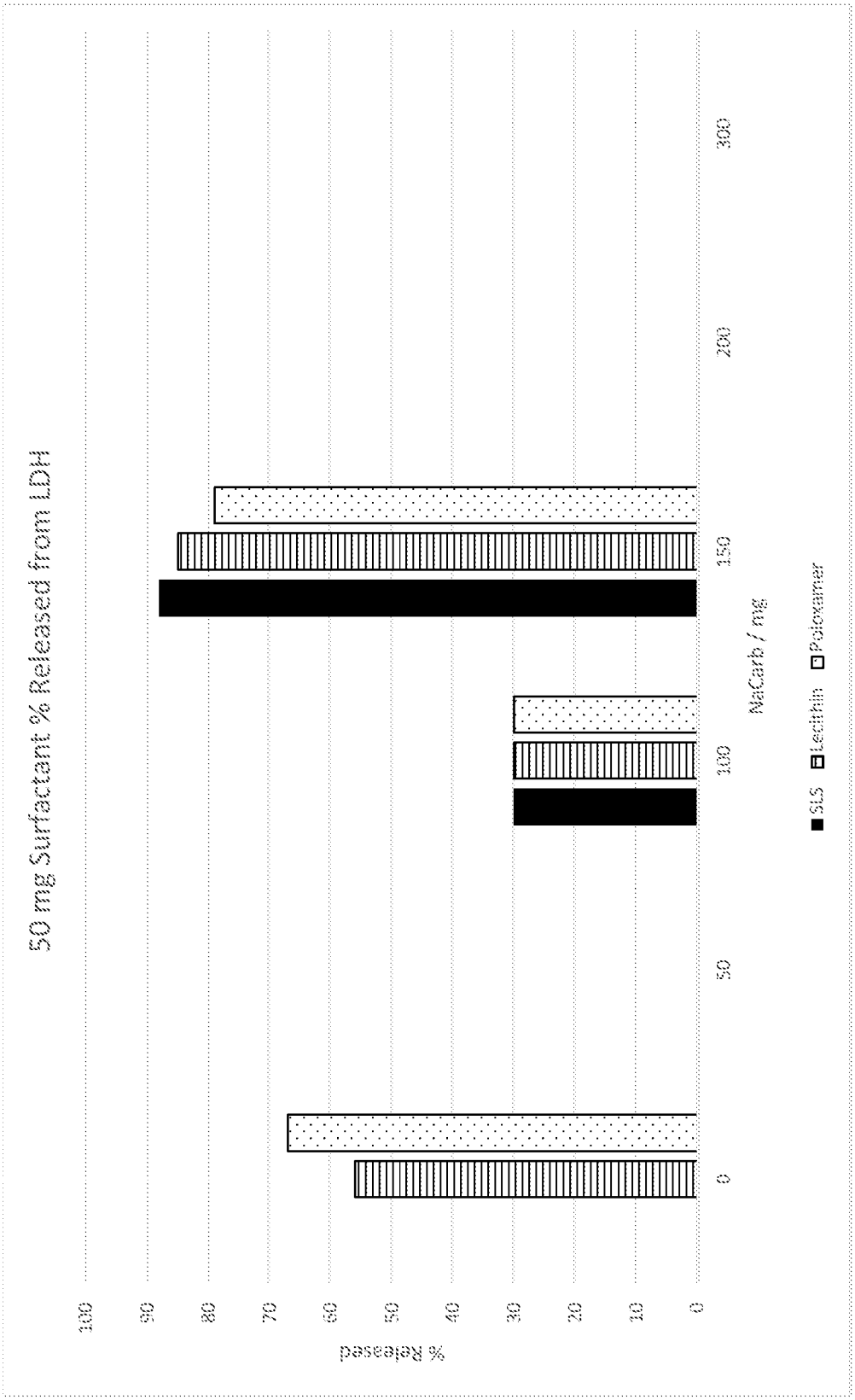
50 mg Surfactant % Released from LDH
% Released
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
300
NaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 18

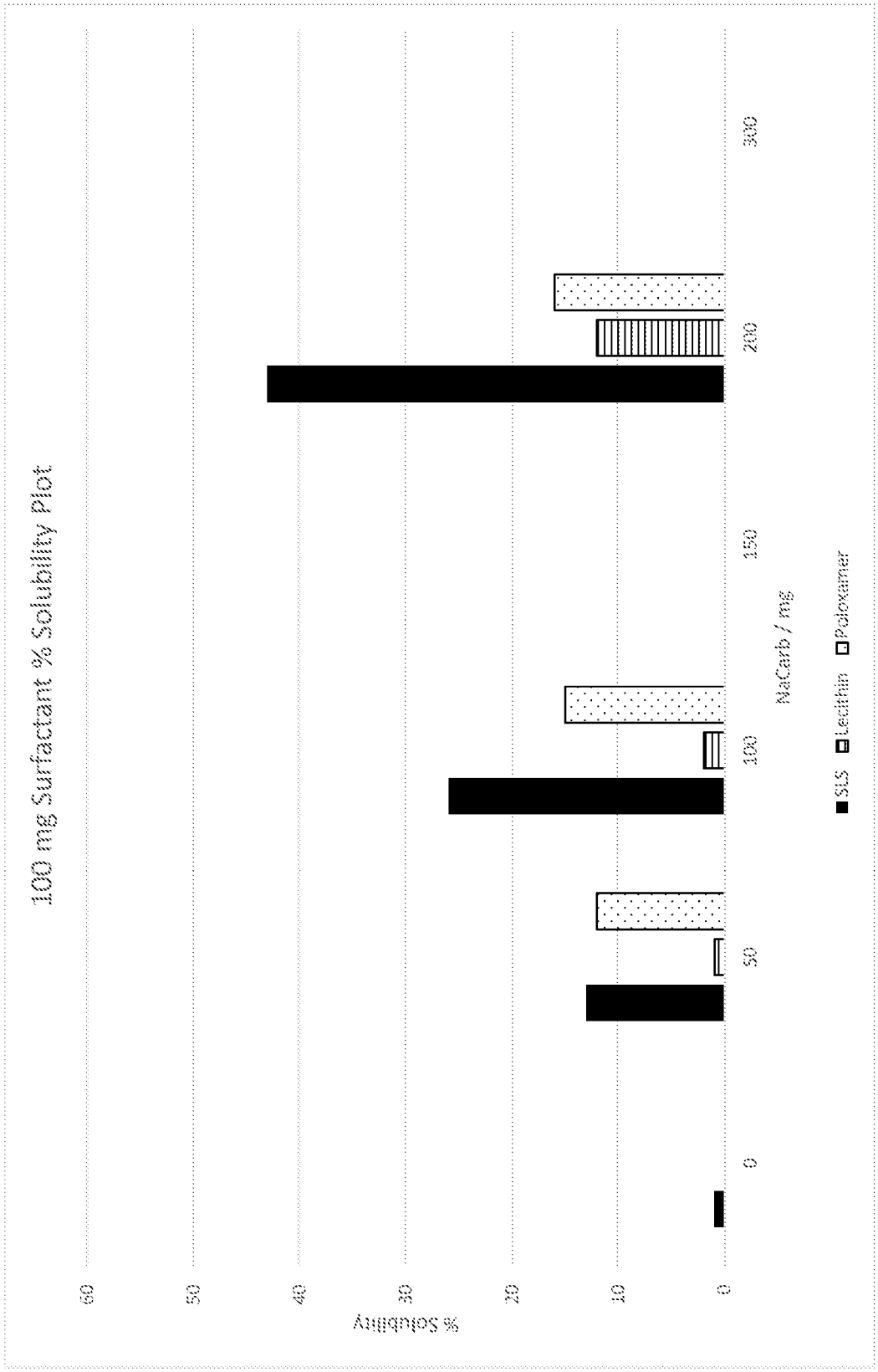
100 mg Surfactant % Solubility Plot
% Solubility
0
10
20
30
40
50
60
0
50
100
150
200
300
NaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 19

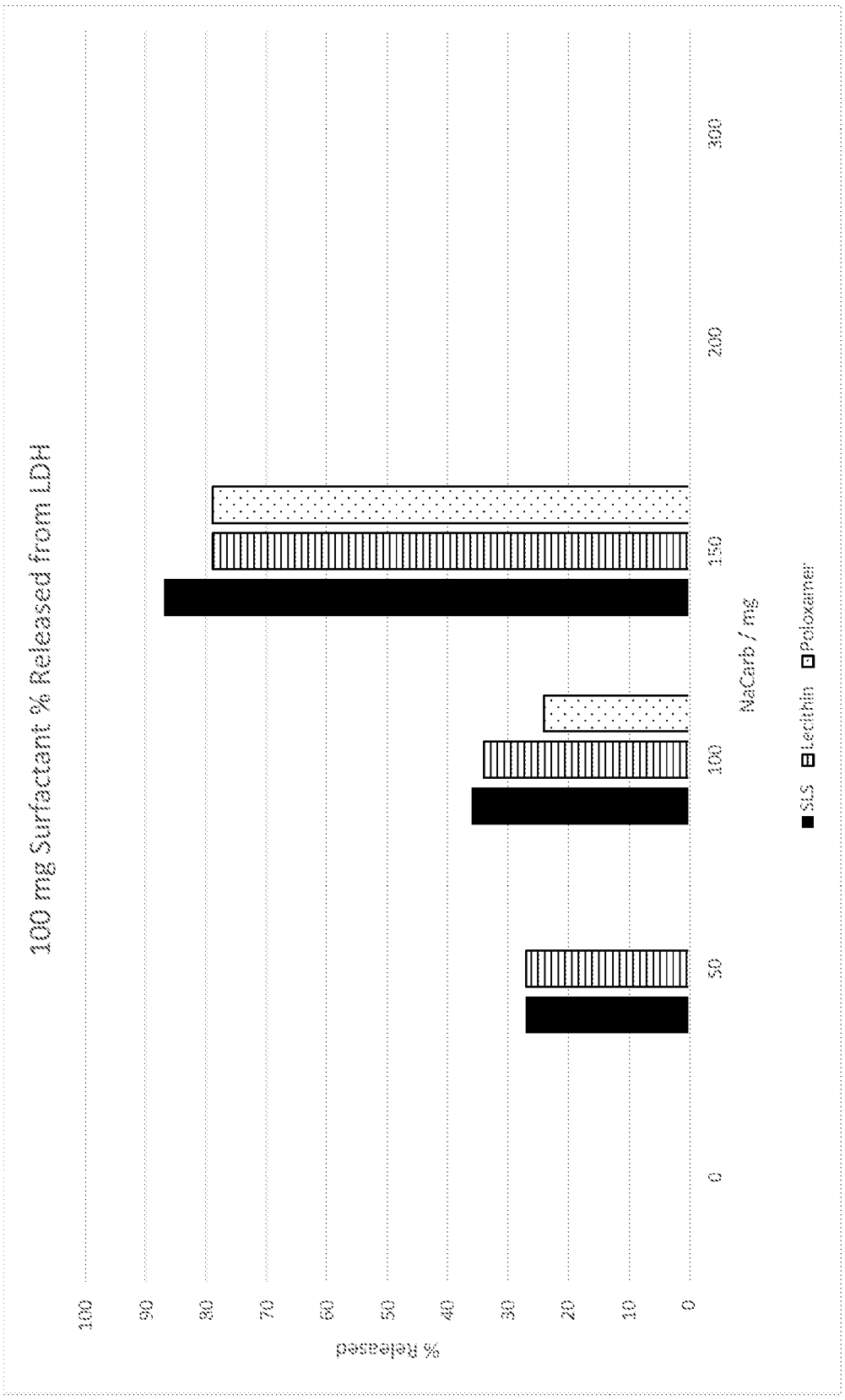
100 mg Surfactant % Released from LDH
% Released
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
300
MaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 20

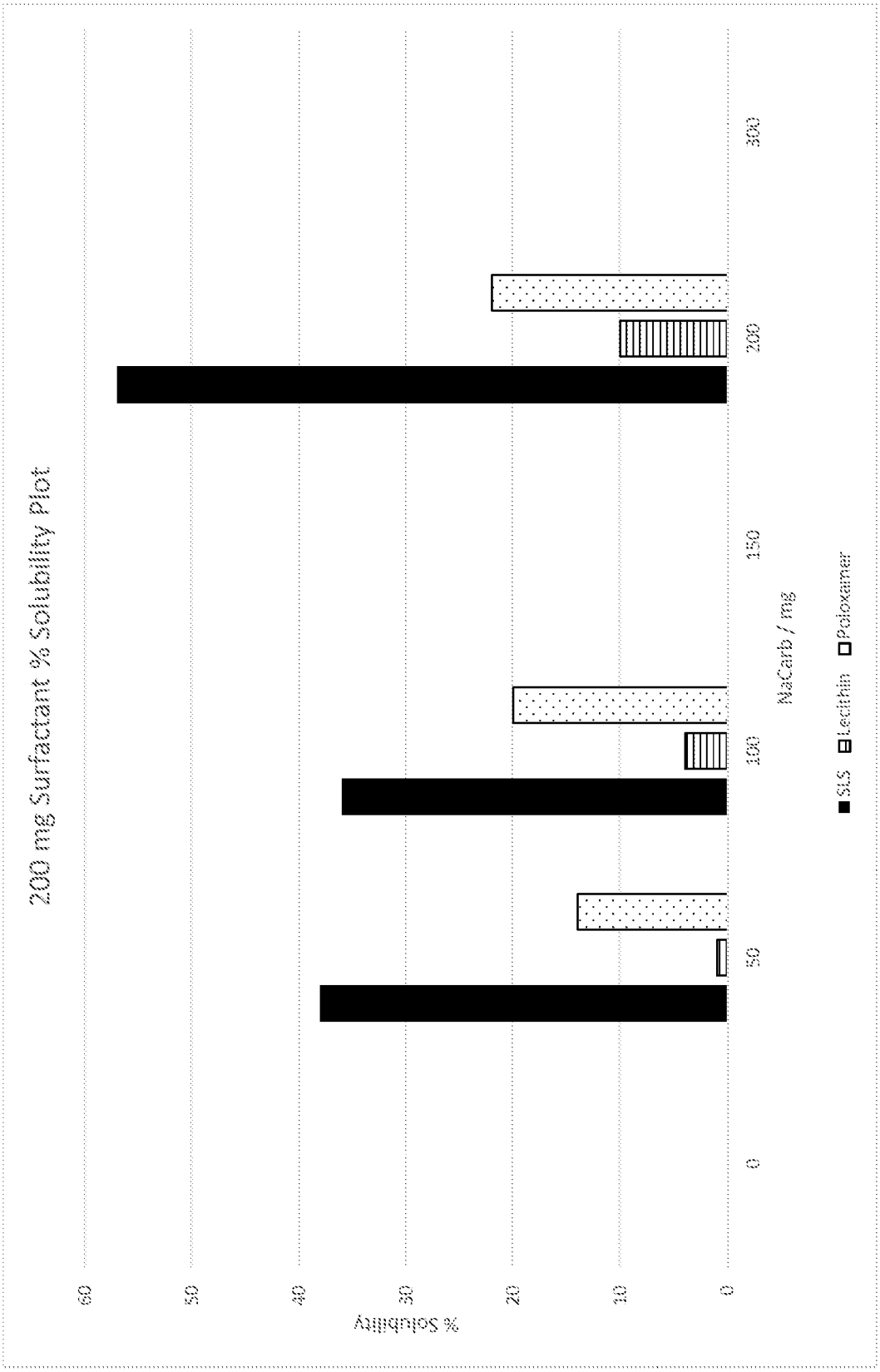
200 mg Surfactant % Solubility Plot
% Solubility
0
10
20
30
40
50
60
0
50
100
150
200
300
NaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 21

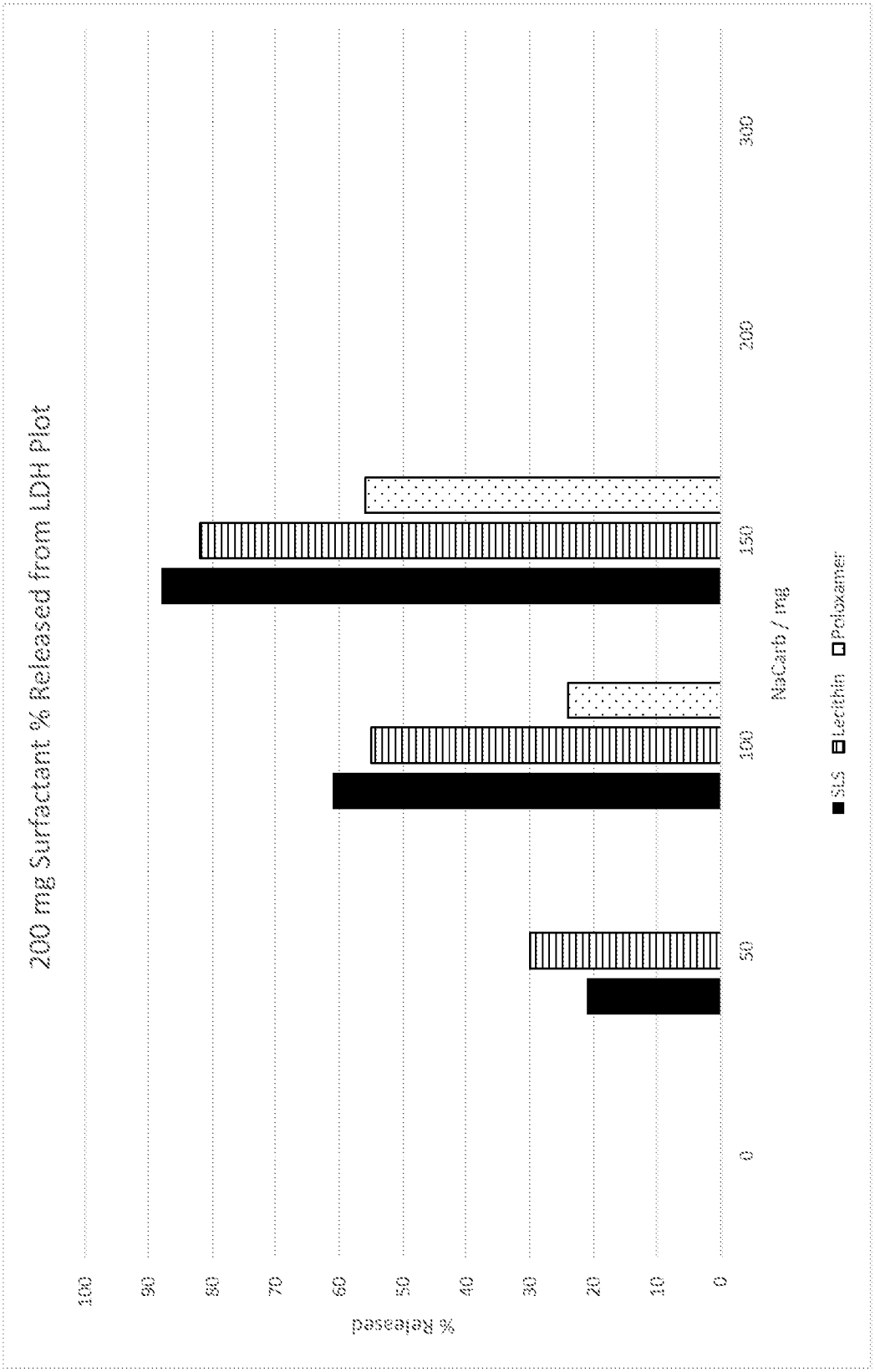
200 mg Surfactant % Released from LDH Plot
% Released
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
300
NaCarb / mg
SLS
Lecithin
Poloxamer

FIGURE 22

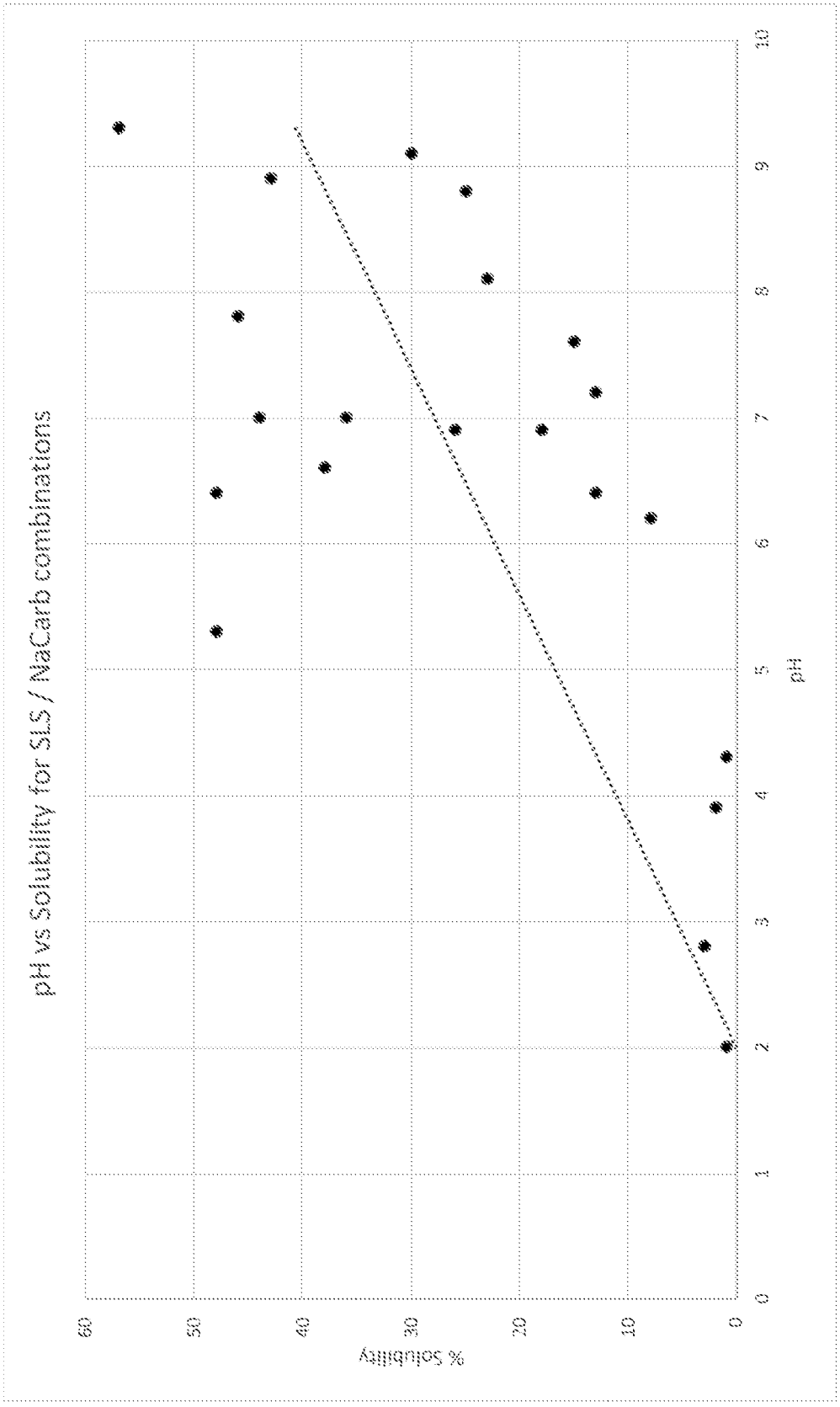
pH vs Solubility for SLS / NaCarb combinations
% Solubility
pH
0
10
20
30
40
50
60
0
1
2
3
4
5
6
7
8
9
10

FIGURE 23

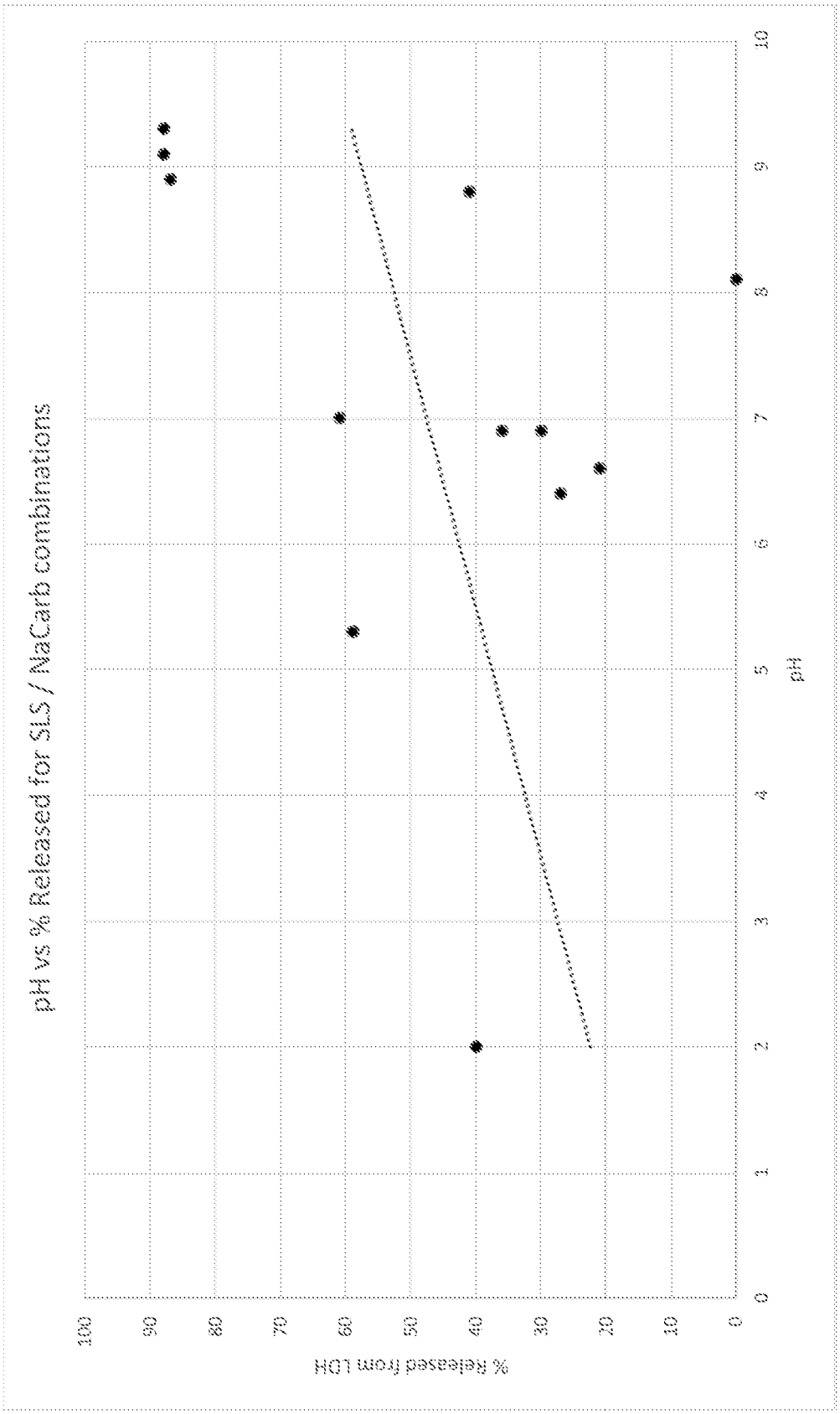
pH vs % Released for SLS / NaCarb combinations
% Released from LDH
pH
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
7
8
9
10

FIGURE 24

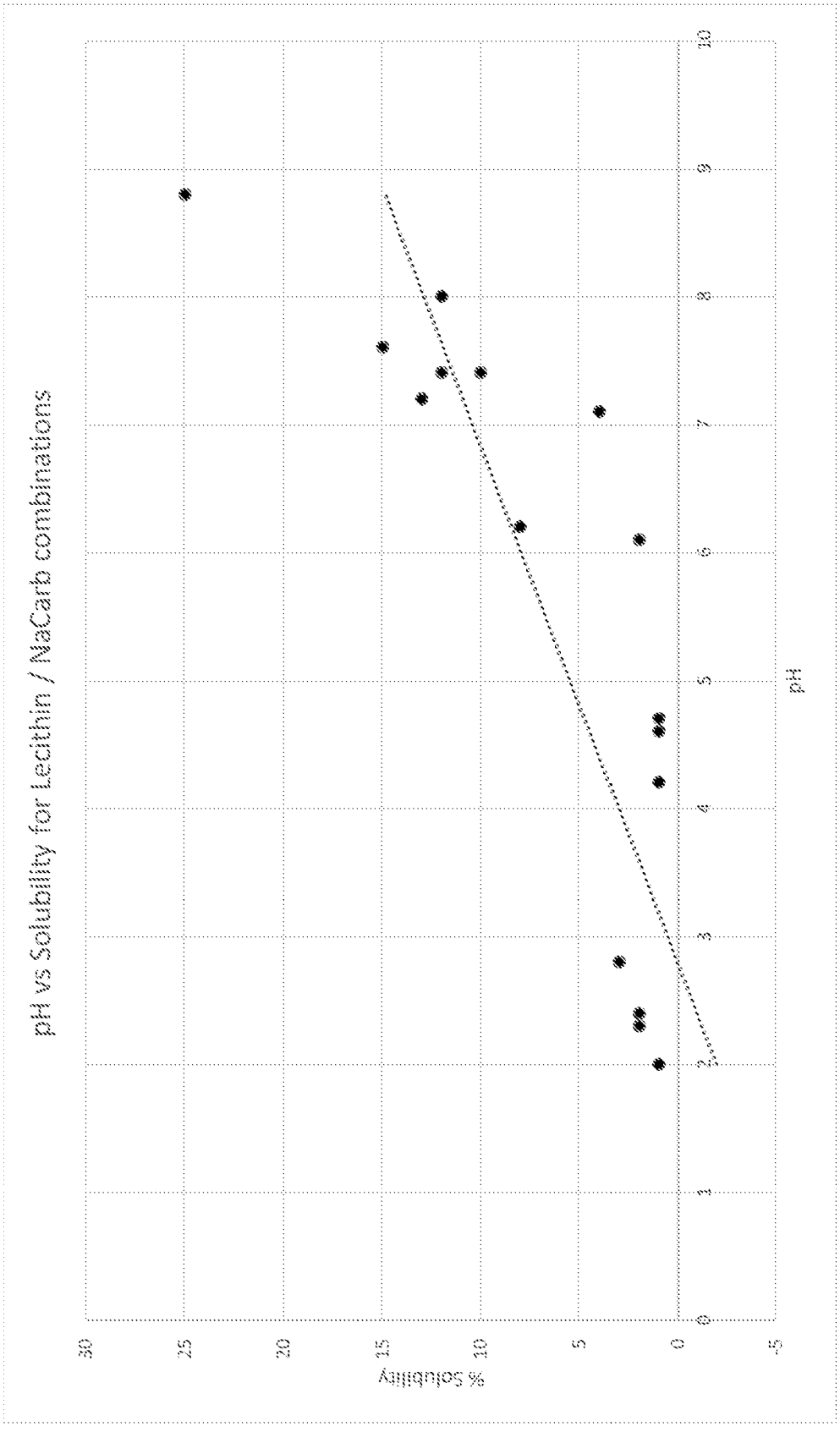
pH vs Solubility for Lecithin / NaCarb combinations
% Solubility
pH
30
25
20
15
10
5
0
-5
0
1
2
3
4
5
6
7
8
9
10

FIGURE 25

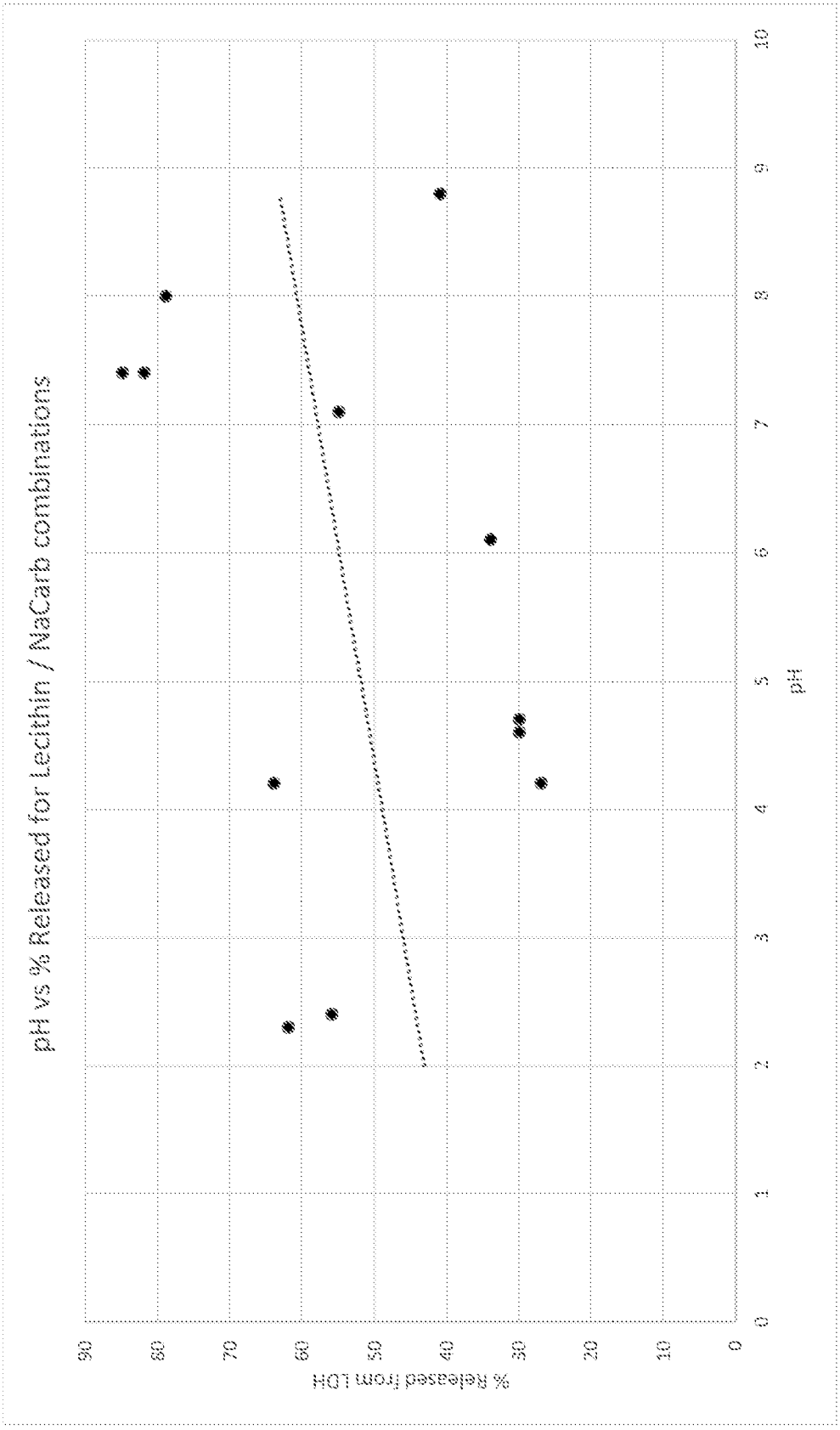
pH vs % Released for Lecithin / NaCarb combinations
% Released from LDH
pH
0
10
20
30
40
50
60
70
80
90
0
1
2
3
4
5
6
7
8
9
10

FIGURE 26

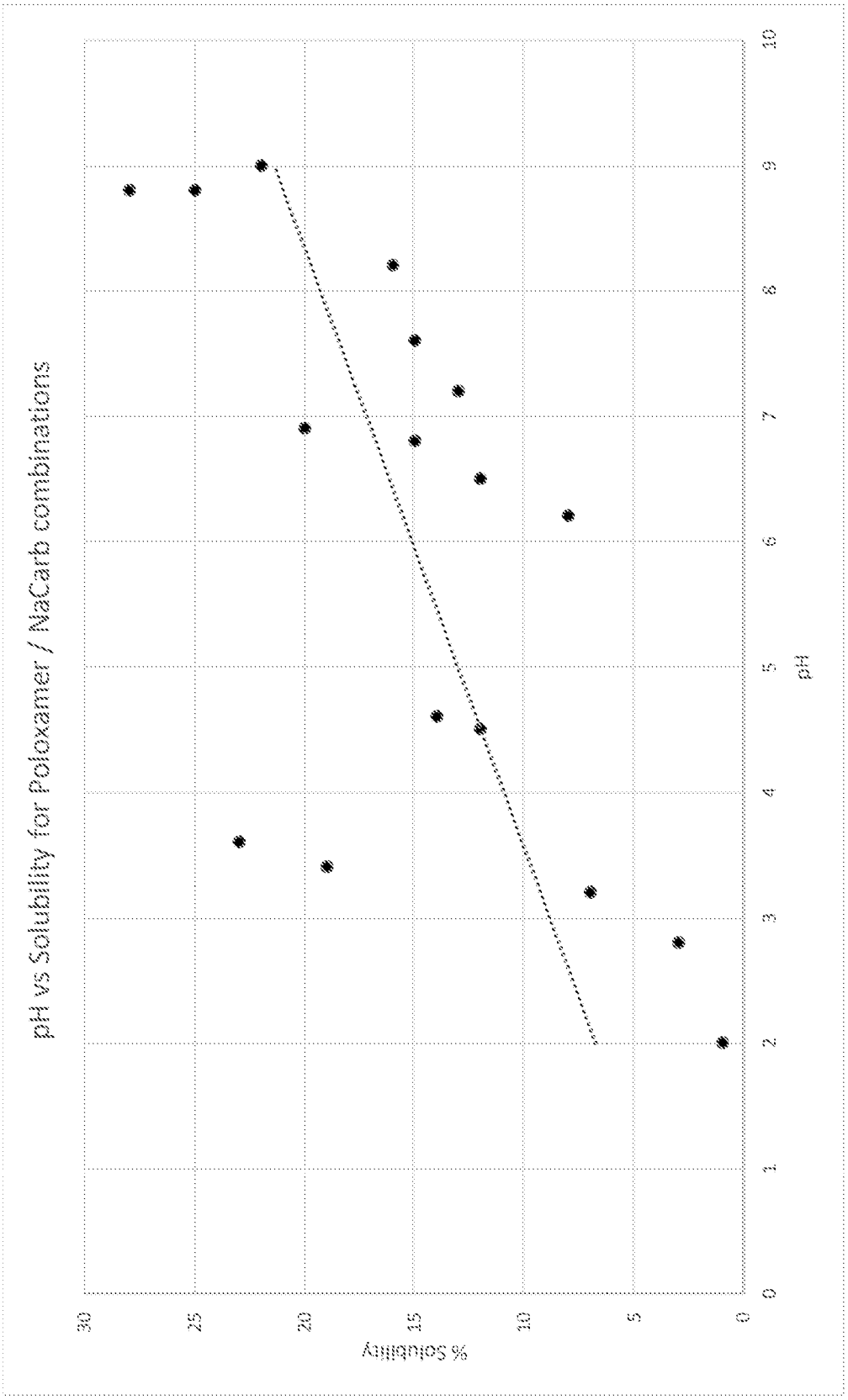
pH vs Solubility for Poloxamer / NaCarb combinations
% solubility
pH
0
5
10
15
20
25
30
0
1
2
3
4
5
6
7
8
9
10

FIGURE 27

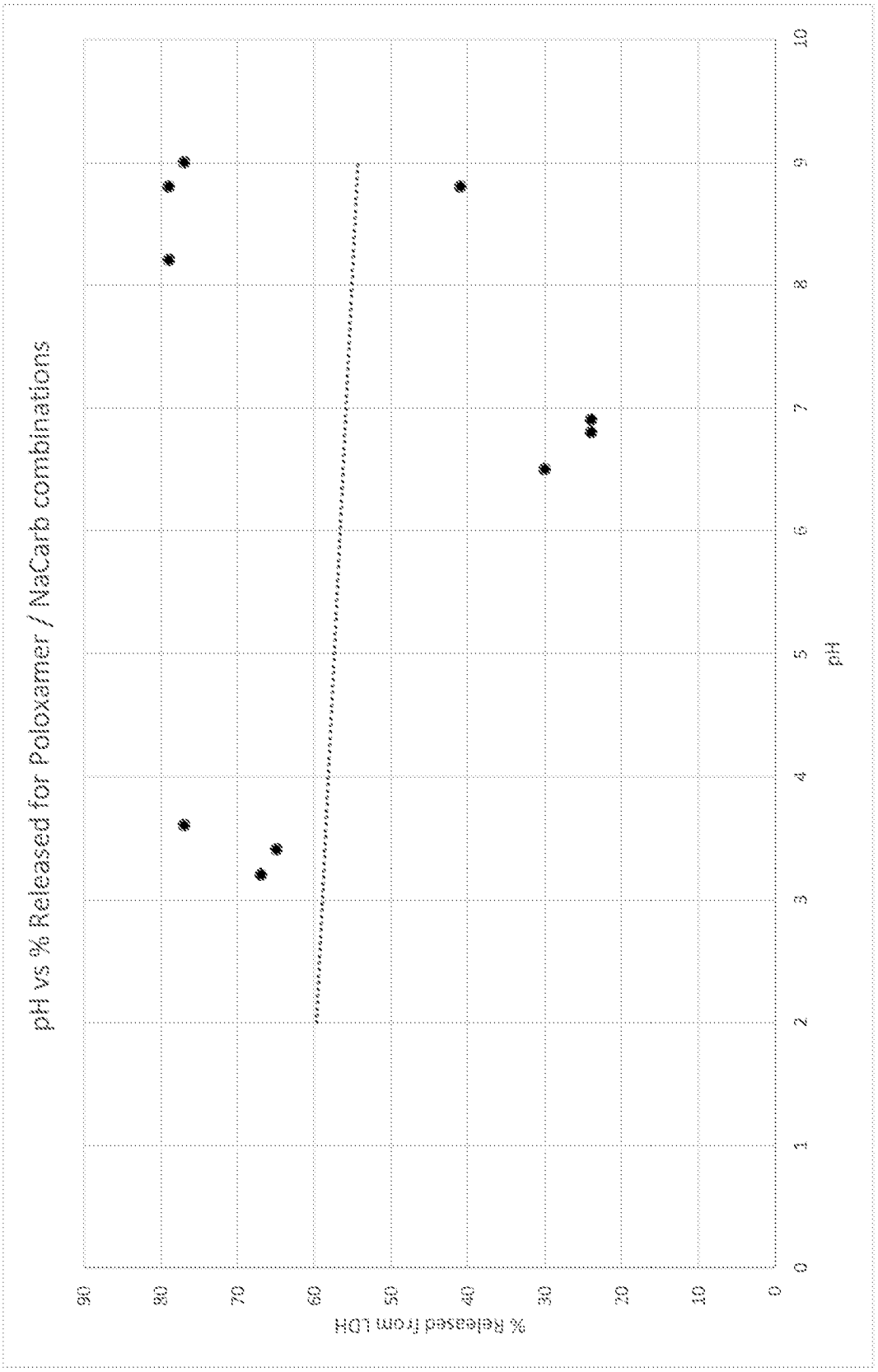
pH vs % Released for Poloxamer / NaCarb combinations
% Released from LDH
pH
0
10
20
30
40
50
60
70
80
90
0
1
2
3
4
5
6
7
8
9
10

FIGURE 28

Sodium Carbonate		0mg (CONTROL)			50mg			100mg			150mg			200mg			300mg		
Surfactants		pH	Solubility %	Solvent Method	pH	Solubility %	Solvent Method	pH	Solubility %	Solvent Method	pH	Solubility %	Solvent Method	pH	Solubility %	Solvent Method	pH	Solubility %	Solvent Method
	0mg													6.92					
None (CONTROL)	0mg	2	1	40	2.8	3		6.2	8		7.2	13		7.6	15		8.8	25	41
	FREE IBU ACID		0	95										6.48	57.03				
SLS	50mg				3.9	2		6.9	18	30				9.1	30	88	8.1	23	
	100mg	4.3	1		6.4	13	27	6.9	26	36				8.9	43	87			
	150mg										7	44							
	200mg				6.6	38	21	7	36	61				9.3	57	88			
	300mg	5.3	48	59	6.4	48											7.8	46	
Lecithin	50mg	2.4	2	56				4.7	1	30				7.4	12	85			
	100mg				4.2	1	27	6.1	2	34				8	12	79			
	150mg	2.3	2	62															
	200mg				4.6	1	30	7.1	4	55				7.4	10	82			
	300mg	4.2	1	64															
Poloxamer 407	50mg	3.2	7	67				6.5	12	30				8.8	28	79			
	60mg	1.7	2.00	60															
	60mg FREE IBU ACID	1.55	4																
	100mg	3.70	3.00	64	4.5	12		6.8	15	24				8.2	16	79			
	100mg FREE IBU ACID	1.56	7					5.9	35	98									
	150mg	3.4	19	65															
	200mg																		
	200mg	3.23	21	64	4.6	14		6.9	20	24				9	22	56			
	200mg FREE IBU ACID	1.47	10													94			
	300mg	3.6	23	77															
Polysorbate	300mg			25															

The following terms are registered trade marks and should be read as such wherever they occur in this document:

Span,
Tween

MODIFIER SYSTEM FOR COMPOSITIONS CONTAINING LAYERED DOUBLE HYDROXIDE

FIELD OF THE INVENTION

The present invention relates to compositions which contain i) layered double hydroxide (LDH) materials intercalated with one or more active anions (LDH-active anion materials), together with ii) a modifier system for controlling the release of the active anion from the LDH-active anion material and for controlling the solubility of the released active anion in acidic media. The present invention particularly relates to compositions in which the active anion in the LDH-active anion material is a pharmaceutically and/or a nutraceutically active anion, and to the use of such compositions in formulations suitable for pharmaceutical and/or nutraceutical applications.

BACKGROUND OF THE INVENTION

A review of layered double hydroxides (LDHs) is given in Chemistry in Britain, September 1997, pages 59 to 62, and briefly, these materials are either mixed hydroxides of monovalent and trivalent metals or mixed hydroxides of divalent and trivalent metals, having an excess of positive charge that is balanced by interlayer anions. Such materials can be represented either by:

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$[M^{I}_{(1-x)}M^{III}_{x}(OH)_2]^{n+}\ A^{z-}_{n/z}.\ yH_2O$ or

$[M^{II}_{(1-x)}M^{III}_{x}(OH)_2]^{x+}\ A^{z-}_{x/z}\ .yH_2O$

where M^{I}, M^{II} and M^{III} are mono-, di- and trivalent cations respectively, that occupy octahedral positions in hydroxide layers; A^{z-} is an interlayer charge-compensating anion; z is an integer; n=2x-1; x is less than 1; and y is ≥ 0.

The methods used in the manufacture of LDH materials are well documented and can include ion exchange, co-precipitation, rehydration, secondary intercalation, re-coprecipitation, and templated synthesis methods, see for example He et al., Struct. Bond, 2006, 119, p.89-119. There are also different methods for preparing LDH materials intercalated with large active anions for example pharmaceutically active molecules and biomolecule, as described in EP0987328(B1), WO2010/089691A1, CN101597474B and EP0550415 A2.

In all end-use applications involving LDH-active anion materials it is important to control the release of the intercalated active anion from the layers of the LDH structure; firstly, to exert

control over the onset and extent of efficacy of the active anion (especially relevant when the active anion is pharmaceutically and/or nutraceutically active), and secondly by controlling active anion release it is possible to improve the safety, toxicity, ease of use and/or ease of handling of the LDH-active anion material.

In their earlier patent application PCT/GB2013/052554, the Applicant describes a process for making improved controlled-release LDH-active anion materials which are able to retain substantially all of the active anion within the LDH matrix whilst in the absence of ion exchange conditions and/or under conditions where the pH is >4. These improved LDH-active anion materials are particularly useful in orally delivered formulations which call for the need to taste-mask an active anion that is poor-tasting, or which causes burn, irritation or some other unacceptable sensation, within the mouth, buccal cavity or larynx; the pH of the mouth is pH 6.2 – 7.6, and the improved LDH-active anion materials are designed to retain the active anion within the LDH structure until after swallowing. Non-standard tablet formulations such as chewable tablets, orally disintegrating tablets, orally disintegrating granules and lozenges which are sucked or chewed are easier for a patient to take than dry tablets, but since the LDH-active anion will remain in the mouth for a few minutes before swallowing, it is beneficial to use the Applicant's earlier improved LDH-active anion materials with taste masking ability in order to reduce non-compliance by patients, particularly within paediatrics patient groups.

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As well as controlling the release of the active anion in the mouth, it is also important to control the release and solubility of the active anion from the LDH lattice when the LDH-active anion material enters the gastrointestinal tract.

EP 1341556(B1) teaches controlling or modifying the release of a pharmaceutically active compound from a drug delivery system comprising LDH materials intercalated with pharmaceutically–active anionic compounds by incorporating a buffer into the formulation, or alternatively, by incorporating an anion-containing non-toxic compound. In use, the anion in the non-toxic compound is described as preferentially displacing the pharmaceutically-active compound from within the layers of the LDH. The non-toxic compounds preferred in this prior art contain carbonate or hydrogen carbonate anions, such as $CaCO_3$, $Ca(HCO_3)_2$, $MgCO_3$ and $Mg(HCO_3)_2$. However, the Applicant has found that these non-toxic compounds produce only a slight increase in the solubility in an acid medium of an acid insoluble active anion, such as ibuprofen, when it is displaced from within the layers of the LDH-active anion material. At this low solubility level it is highly unlikely that it will be possible to achieve a pharmacokinetic profile comparable with that obtained for the Ibuprofen free acid.

Furthermore, contrary to the teachings in EP1341556(B1), the Applicant has evidence to indicate that metal carbonates do not promote much more active anion to be released from within the layers of the LDH matrix, than the amount which is released when a metal carbonate is not present.

As discussed by B. S. Sekhon in J. Pharmaceutical Technology Research and Management, vol. 1 2013, 11-36: "Surfactants: Pharmaceutical and Medicinal Aspects", surfactants are known to be components of many pharmaceutical products, for example i) to solubilise hydrophobic drugs in aqueous media, ii) as components of emulsions, iii) as surfactant self-assembly vehicles for oral and transdermal drug delivery, iv) as plasticisers in semisolid delivery systems and v) as agents to improve drug absorption and penetration. Non-ionic surfactants such as ethers of fatty alcohols are most commonly used in pharmaceuticals and serve as emulsifiers, wetting agents, solubilisers and dispersants. Further, D. Ramya Devi et al have compiled a review of the different attributes of poloxamer and its application in drug delivery in J. Pharm. Sci. & Res. Vol. 5(8), 2013, 159-165: "Poloxamer: A Novel Functional Molecule For Drug Delivery and Gene Therapy".

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However, a research paper by P. Dewland et al, BMC Clinical Pharmacology 2009, 9:19: "Bioavailability of ibuprofen following oral administration of standard ibuprofen, sodium ibuprofen or ibuprofen acid incorporating poloxamer in healthy volunteers" concludes that poloxamer 407 surfactant is ineffective to enhance the dissolution and bioavailability of poorly water soluble drugs, including ibuprofen.

Moreover, although several other studies report an increase in the solubility of ibuprofen in acidic media as a result of the presence of a poloxamer 407 or 188 (non-ionic surfactants), this is disclosed as only being possible when the two ingredients are in the form of a binary solid dispersion, for example, R.P Dugar et al "Preparation and Characterization of ibuprofen-Poloxamer 407" in AAPS PharmSciTech 2016 Jan 27 [Epub ahead of print], and M. Newa et al "Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188", International Journal of Pharmaceutics, Volume 343, Issues 1–2, 1 October 2007, Pages 228–237. Further, the enhanced ibuprofen solubility is reported in these papers to be due to the formation of eutectics between the ibuprofen and the poloxamer, rather than due to the presence of the surfactant per se. The loss of ibuprofen crystallinity in the fused ibuprofen/poloxamer mixture was confirmed by XRPD, and is disclosed to be the principle cause of the increased solubility.

Meanwhile, Hoo-Kyun Chi and Sung-Hyun Park report in the International Journal of Pharmaceutics 321 (2006) 35-41: "The effects of surfactants on the dissolution profiles of poorly water-soluble acidic drugs", that the dissolution of acidic drugs such as mefenamic acid, nimesulfide and ibuprofen is substantially enhanced in a medium containing cetyltrimethylammonium bromide (CTAB), a cationic surfactant, as compared against sodium lauryl sulfate (SLS), an anionic surfactant, or polysorbate 80, a non-ionic surfactant.

Notwithstanding the prior art discussed above, there is a need 1) to control the amount of active anion which is released from between the layers of LDH in an LDH-active anion material, and also 2) to improve the solubility of the released active anion in acidic media, particularly in the case of poorly water soluble active anions such as ibuprofen. Controlling release to increase the amount of active anion released and increasing its solubility in the stomach may lead to faster and increased absorption. Conversely, controlling release to reduce the amount released in the stomach may provide for slower absorption.

STATEMENT OF THE INVENTION

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The aim of the present invention is to provide compositions which contain LDH-active anion materials and which enable the controlled release of the active anion from within the LDH layers, when in an acidic media designed to represent the conditions found in a fasted human stomach. Advantageously, the active anion is a pharmaceutically and/or nutraceutically active anion.

It is desirable that the compositions of the present invention control the release of the active anion by effecting an increased amount of active anion to be released from within the LDH layers of an LDH-active anion material, relative to the amount released by the LDH-active anion alone, in an acidic media.

Another key goal of the present invention is to provide compositions which contain LDH-active anion materials and which enable the increased solubilisation of the active anion in acidic media.

Thus, a further aim is to provide compositions which contain LDH-active anion materials and from which release of the active anion is controlled so as to exhibit a fast and increased absorption of the active anion in the gastrointestinal (GI) tract.

The present invention, therefore, provides a composition comprising: i) one or more LDH-active anion materials comprising an LDH matrix intercalated with an active anion, and ii) a modifier system comprising a surfactant, in combination with sodium carbonate; wherein the active anion is ibuprofen and the composition has a weight ratio of the LDH matrix: sodium carbonate: the surfactant, of 1: 1: 0.25 to, wherein the surfactant is selected from poloxamer, lecithin and SLS.

As demonstrated in the specific examples below, the present invention provides a composition which contains a modifier system which is capable of 1) controlling the total amount of active anion released from the LDH matrix under acidic conditions designed to represent the conditions found in a fasted human stomach, compared against the amount which is released when the modifier system is absent or when a surfactant is used alone and 2) increasing amount of active anion which is dissolved in the acidic medium, compared against the amount which is dissolved when a surfactant is used alone or when a metal salt is used alone or when the modifier system is absent.

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In one embodiment, the present invention provides a composition which contains a modifier system which is capable of promoting a significant increase in the amount of active anion which is released and dissolved in acidic media that is designed to represent the conditions found in a fasted human stomach, when compared against the amount of active anion which is released and dissolved under comparable conditions in the presence of either a surfactant alone or when in the presence of a metal salt alone or when the modifier system is absent.

The Applicant has unexpectedly found that the combination of a surfactant and sodium carbonate used in the modifier system of the present invention, shows synergistic activity towards the release and solubility of an active anion in acidic media. Further, that this synergistic activity allows for the amount of surfactant to be reduced whilst maintaining the desired active anion release and solubility in acidic media. A reduction in the amount of surfactant is particularly advantageous for pharmaceutical and nutraceutical formulations where high levels of surfactant would be expected to be unpalatable due to their soapy taste, and depending on the surfactant used, could have an undesirable safety profile. Not only this, processing and formulation difficulties are also expected with high surfactant levels, for example it is likely to be difficult to ensure that the ingredients are uniformly blended, and there may be an issue with forming tablets with the desired hardness.

The modifier system preferably comprises one or more surfactants selected from:

1) anion surfactants such as carboxylates: alkyl carboxylates (e.g. fatty acid salts), carboxylate fluoro-surfactants; sulfates: alkyl sulfates (e.g. sodium lauryl sulfate), alkyl ether sulfates (e.g. sodium laureth sulfate); sulfonates: docusates (e.g. dioctyl sodium sulfosuccinate), alkyl benzene sulfonates; phosphate esters: alkyl aryl ether phosphates and alkyl ether phosphates.

2) Zwitterionic (amphoteric) surfactants, which can be anionic, cationic or non-ionic depending on the pH of the solution they are in. Examples include: $RN^+H_2CH_2COO^-$, $RN^+(CH_3)_2CH_2CH_2SO_3^-$, phospholipids such as phosphatidylcholine (Lecithin).

3) Cationic surfactants which bear a positive charge for example $RN^+H_3Cl^-$ or $RN^+(CH_3)_3Cl^-$.

4) Non-ionic surfactants which are uncharged. Examples include: polyol esters (e.g. glycol, glycerol esters, sorbitan and sorbitan derivatives such as fatty acid esters of sorbitan (Spans) and their ethoxylated derivatives (Tweens)), polyoxyethylene esters and poloxamers.

The Applicant has found that anionic, zwitterionic and non-ionic surfactants are particularly useful in the modifier system used in the composition of the present invention.

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Contrary to what would be expected from the known interactions between a surfactant and an active anion, as described above in relation to various prior art documents, the surfactants in the modifier system used in the present invention do not merely act to increase the solubility of the active anion once it has been released. Indeed, as the results presented below in the specific examples demonstrate, not all surfactants promote an increase in the solubility of the active anion, and further, the presence of a surfactant has a strong influence over the amount of active anion which is released.

Preferred surfactants to be used in the modifier system of the present invention, therefore, are those which intercalate and/or interact with the LDH portion of the LDH-active anion material. Anionic surfactants such as sodium lauryl sulfate work very effectively and are believed to interact with the cationic layers of the LDH, however, the Applicant has unexpectedly found that poloxamers, which are non-ionic surfactants and lecithin, which is a zwitterionic surfactant, also interact in some way with the LDH to cause the active anion to be released from the LDH matrix, thus making these surfactants surprisingly highly effective in the modifier system used in the compositions of the present invention. In pharmaceutical applications, irritant and cancer concerns arise in respect of certain surfactants, for example sodium lauryl sulfate, therefore poloxamer and lecithin are especially preferred in compositions which are to be used in pharmaceutical and/or nutraceutical formulations.

Further, for taste masked formulations, poloxamer is preferred since high levels of lecithin have an unpleasant odour. Poloxamer 407 is found to be particularly useful.

In the one or more LDH-active anion materials the term "active anion" includes any molecule that is anionic (i.e. a molecule with a negative charge). An anion is interpreted to be "active" in the sense that compounds containing said anion produce a chemical, physical, physiological, nutraceutical or pharmaceutical effect which is preferably recognised in an animal or human body. Suitable active anions may be simple anions or they may be larger and/or have more complex structures. Compounds which contain an active anion may include additives used in medicaments, food supplements and vitamin supplements nutraceuticals and pharmaceuticals.

Preferred compounds which contain an active anion are those which produce a pharmaceutical effect, and these pharmaceutical compounds may include the classes of NSAIDS, gaba-analogues, antibiotics, statins, angiotensin-converting enzyme (ACE) inhibitors, antihistamines, dopamine precursors, anti-microbials, psychostimulants, prostaglandins, anti-depressants, anti-convulsants, coagulants, anti-cancer agents, immunosuppressants and laxatives.

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It is believed that the compositions of the present invention will be particularly advantageous in relation to acidic pharmaceutical compounds and/or those which are largely insoluble in acid media, for example ibuprofen.

The modifier systems used in the compositions of the present invention are able to control the amount of active anion released to be in the range 56% to 88% (compared against 40% release obtained in the absence of a modifier system and 41% release obtained in the presence of 300mg sodium carbonate without a surfactant (200mg LDH matrix)) in acidic media, and are able to increase the solubility of the active anion which is released from 1 to 57% (compared against the 0.9% release obtained in the absence of a modifier system and 25% in the presence of 300mg sodium carbonate without a surfactant (200mg LDH matrix)) in acidic media. The modifier system used in the compositions of the present invention has a weight ratio of the LDH matrix : sodium carbonate : the surfactant, of 1 : 1 : 0.25 to 1.

Surprisingly, however, the amount of the LDH matrix relative to the amount of sodium carbonate, is found to be highly influential in giving the flexibility in the controlled release of the active anion from the LDH layers and also in increasing the solubility of the released active anion in acidic media, provided an amount of surfactant is also present.

The modifier system is designed to increase the amount of active anion released from the LDH matrix (compared against the amount which is released when the one or more surfactant compounds are present in the absence of sodium carbonate), the preferred weight ratio of LDH matrix : sodium carbonate : surfactant is 1 : 1 : 0.25 to 1.

An especially preferred composition of the present invention comprises a modifier system which comprises 1 part by weight of LDH matrix, at least 0.5 parts by weight of sodium carbonate and 1 part by weight of surfactant. An example of such a composition is: 400mg LDH-ibuprofen (contains 200mg LDH), at least 100mg sodium carbonate and 200mg of one or more surfactants selected from sodium lauryl sulfate, lecithin and poloxamer.

In a further embodiment, the present invention provides a method for 1) controlling the total amount of active anion released from the LDH matrix under acidic conditions designed to represent the conditions found in a fasted human stomach, and 2) increasing amount of released active anion which is dissolved in the acidic medium, the method comprising the step of forming a composition comprising: i) one or more LDH-active anion materials comprising an LDH matrix intercalated with an active anion, and ii) a modifier system comprising a surfactant, in combination with sodium carbonate; wherein the active anion is ibuprofen and the composition has a weight ratio of the LDH matrix: sodium carbonate: the surfactant, of 1: 1: 0.25 to, wherein the surfactant is selected from poloxamer, lecithin and SLS , wherein the amount of released active anion which is dissolved in the acidic medium is increased relative to both the amount which is dissolved when the surfactant is used in the absence of the metal salt and the amount which is dissolved when the one or more metal salts is used in the absence of the one or more surfactants.

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Any suitable method may be used to determine the % release of the active anion and also the % solubility of the released active anion in an acid medium. In one convenient method described below, % release and % solubility were both determined after 15 minutes, although a longer or a shorter time may be used if desired, 15 minutes was chosen because this is the approximate time for gastric emptying in a fasted stomach. 0.05M Hydrochloric acid was chosen as the acid medium as this is a reasonable approximation of the acidity found in the human stomach, however, any other suitable medium may be used instead.

The compositions of the present invention are useful in a wide range of storage, carrier and delivery system applications for pharmaceutical and nutraceutical applications, especially where it is required to control the release of the active anion. The compositions of the present invention advantageously allow for control of the release under the acid conditions of

the fasted human stomach, of the active anion from LDH-active anion materials which are highly resistant to leaching, for example when substantially all of the active anion is retained within the LDH matrix whilst the absence of ion exchange conditions and/or under conditions of above pH 4.

Therefore the present invention provides for the use of a composition as a carrier, a storage system and/or in a delivery system, said composition comprising i) one or more LDH-active anion materials, and ii) a modifier system comprising a surfactant, in combination with sodium carbonate; wherein the active anion is ibuprofen and the composition has a weight ratio of the LDH matrix: sodium carbonate: the surfactant, of 1: 1: 0.25 to, wherein the surfactant is selected from poloxamer, lecithin and SLS.

The present invention also provides for the use of the composition of the present invention in oral pharmaceutical and/or nutraceutical applications, and in a further aspect, the compositions of the present invention are for use in the preparation of pharmaceutical and/or nutraceutical formulations.

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Therefore, the present invention provides a formulation comprising a composition containing i) one or more LDH-active anion materials comprising an LDH matrix intercalated with an active anion, and ii) a modifier system comprising a surfactant, in combination with sodium carbonate; wherein the active anion is ibuprofen and the composition has a weight ratio of the LDH matrix: sodium carbonate: the surfactant, of 1: 1: 0.25 to, wherein the surfactant is selected from poloxamer, lecithin and SLS, wherein the formulation is selected from dry granules, tablets, caplets, orally disintegrating tablets, orally disintegrating granules, lozenges, films, capsules, powders, effervescent formulations and buccal and sub-lingual formats.

Advantageously the formulation according to the present invention comprises a composition which allows for the control of release of the active anion from the LDH-active anion material contained therein.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will now be described with reference to the following figures in which:

Figure 1 is a graph of geometric mean concentration against time to compare the Brufen® single dose PK with that obtained for LDH-ibuprofen.

Figure 2 is a graph of % solubility v the amount of sodium carbonate, for sodium lauryl sulfate (SLS) surfactant;

Figure 3 is a graph of % solubility v the amount of sodium carbonate, for lecithin surfactant;

Figure 4 is a graph of % solubility v the amount of sodium carbonate, for poloxamer 407 surfactant;

Figure 5 is a graph of % active anion released v the amount of sodium carbonate, for sodium lauryl sulfate (SLS) surfactant;

Figure 6 is a graph of % active anion released v the amount of sodium carbonate, for lecithin surfactant;

Figure 7 is a graph of % active anion released v the amount of sodium carbonate, for poloxamer 407;

Figure 8 is a bar graph showing % solubility v amount of sodium lauryl sulfate (SLS) surfactant;

Figure 9 is a bar graph showing % solubility v amount of lecithin surfactant;

Figure 10 is a bar graph showing % solubility v amount of poloxamer 407 surfactant;

Figure 11 is a bar graph showing % released v amount of sodium lauryl sulfate (SLS) surfactant;

Figure 12 is a bar graph showing % released v amount of lecithin surfactant;

Figure 13 is a bar graph showing % released v amount of poloxamer 407 surfactant;

Figure 14 is a graph showing the % solubility for 0 mg surfactant v amount of sodium carbonate;

Figure 15 is a graph showing % release for 0 mg surfactant v amount of sodium carbonate;

Figure 16 is a graph showing the % solubility for 50 mg surfactant v amount of sodium carbonate;

Figure 17 is a graph showing % release for 50 mg surfactant v amount of sodium carbonate;

Figure 18 is a graph showing the % solubility for 100 mg surfactant v amount of sodium carbonate;

Figure 19 is a graph showing % release for 100 mg surfactant v amount of sodium carbonate;

Figure 20 is a graph showing the % solubility for 200 mg surfactant v amount of sodium carbonate;

Figure 21 is a graph showing % release for 200 mg surfactant v amount of sodium carbonate;

Figure 22 is a graph showing pH v % solubility in sodium lauryl sulfate (SLS) with sodium carbonate;

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Figure 23 is a graph showing pH % release in sodium lauryl sulfate (SLS) with sodium carbonate;

Figure 24 is a graph showing pH v % solubility in lecithin with sodium carbonate;

Figure 25 is a graph showing pH % release in lecithin with sodium carbonate;

Figure 26 is a graph showing pH v % solubility in poloxamer 407 with sodium carbonate;

Figure 27 is a graph showing pH % release in poloxamer 407 with sodium carbonate; and

Figure 28 is a table of the % solubility and % release results obtained in Experiment 3.

DETAILED DESCRIPTION

Experiment 1 – Comparing The *In Vitro* and *In Vivo* Rate Of Release Of 400 mg Ibuprofen from LDH-Ibuprofen Tablet Against The Rate Of Release Of Ibuprofen from Brufen®.

The *in vitro* dissolution testing of the rate of release of ibuprofen from a tablet formulation of LDH-ibuprofen (400mg ibuprofen) compared against rate of release of ibuprofen from Brufen®, a commercially available tablet formulation containing 400mg ibuprofen, showed comparable release of >95% after 5 minutes.

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However, in a clinical study to compare the Pharmacokinetic (PK) performance of a tablet formulation of LDH-ibuprofen (400mg ibuprofen) against the performance of Brufen®, a commercially available tablet formulation containing 400mg ibuprofen, the LDH-ibuprofen tablet failed to show bioequivalence to the Brufen® product. As illustrated in Figure 1, the PK results show comparable AUC and time to maximum plasma concentration (Tmax). The rapid ibuprofen absorption in the first hour in the stomach for the LDH-ibuprofen tablet is comparable with the rate of absorption for Brufen®. Following this however, a slower more prolonged ibuprofen release from the LDH-ibuprofen tablet is observed as the remaining ibuprofen ion-exchanges out of the LDH matrix as it travels down the GI tract. This results in a C_{max} for the LDH-ibuprofen tablet being reduced to 65% of that observed with Brufen®.

The differences between the *in vitro* and *in vivo* results may be due to the use of a phosphate buffer in the *in vitro* dissolution testing which may be promoting ion-exchange. This theory was tested and is apparently confirmed as different release rates are obtained depending on which buffer is used and at what concentration. In addition, dissolution testing using FaSSIF and FeSSIF buffers (maleate buffers which are more reflective of the stomach and intestines) showed that these buffers have insufficient buffering capacity to promote ion exchange and hence slowed down the release of the drug from the LDH matrix.

Experiment 2: Testing Different Agents on LDH-Ibuprofen To Determine Their Effect On The Amount Of Ibuprofen Dissolved

Experimental Conditions

400 mg LDH-ibuprofen (equivalent to 200 mg ibuprofen) is added to 0.05M hydrochloric acid (50ml) with various agents to test their effect in any on the rate of ibuprofen release. The mixture is stirred for 15 minutes and then sampled HPLC for analysis.

TABLE 1

	AGENT @ 100mg			AGENT @ 300mg		
AGENT	**pH**	**DISSOLVED (%)**	**mg/mL**	**pH**	**DISSOLVED (%)**	**mg/mL**
NONE (CONTROL)	2.0	1	0.04	6.1	4	0.14
$MgCO_3$	2.6	2	0.06	-------	-------	-------
$Na(CO_3)_2$	6.2	8	0.33	-------	-------	-------
$NaHCO_3$	2.7	2	0.09	-------	-------	-------
$CaCO_3$	2.5	1	0.05	3.6	2	0.08
$Mg(OH)_2$	2.3	1	0.04			
Na_2SO_4	3.3	2	0.08	3.7	1	0.05
Sodium Lauryl Sulfate	4.3	1	0.03	5.3	48	1.91
$Ca_3(PO_4)_2$,	3.2	1	0.04	3.7	1	0.05
$CaHPO_4$	3.2	1	0.03	3.6	1	0.03

Looking at the above results, there does not appear to be any linear relationship between pH and solubility, e.g. 100mg sodium carbonate and 300mg of magnesium carbonate each give a pH of approximately 6, but sodium carbonate dissolved about 8% ibuprofen, whereas

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magnesium carbonate only dissolved about 3.5% ibuprofen. Consequently, contrary to the teaching in EP1341556B, the rate of ibuprofen release from the LDH layers is not merely a matter of ensuring that the pH is at a particular level. Also, as the above results demonstrate, the addition of sodium carbonate surprisingly improves the rate of ibuprofen release to a greater extent than would be expected from the results obtained for the carbonates disclosed in EP1341556B. The two calcium phosphate materials, although similar to the chemicals used in a phosphate buffer, gave poor dissolution whereas adding the surface active agent sodium lauryl sulfate dissolved the highest amount of ibuprofen at 47.6%.

The following two test methods have been developed to test the efficacy of the proposed modifier systems according to the present invention. It is particularly instructive to use the two methods in parallel when the modifier system contains a combination of constituents which alter both the solubility and the release of the ibuprofen:

1) **SOLVENT SYSTEM METHOD** For Determining The Total Amount Of Ibuprofen Released From The LDH

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This method determines the total amount of ibuprofen that is released from the LDH matrix.

Method:

LDH-ibuprofen (200mg dose of ibuprofen) and modifier agent (where used, in the amounts shown in Table 2), are added to 0.05M HCl (50 mL) and the resulting solution stirred for 15 minutes. After 15 minutes, methanol (50mL) followed by a 1:1 mixture of methanol and water (150mL) are added to the stirred LDH-ibuprofen/HCl solution. A sample is then removed for analysis to determine the total amount of ibuprofen (dissolved and undissolved) which is released into the HCl solution. Further dilution is conducted as required.

2) **SOLUBILITY METHOD** For Determining The Amount Of Ibuprofen Dissolved

The solubility method determines how much of the free ibuprofen dissolves in the acid medium. The medium is designed to reflect the conditions found in a fasted human stomach. The difference between the amount determined by method 1 and the amount determined by method 2 is the amount of ibuprofen which formed as a precipitate.

LDH-ibuprofen (200mg dose of ibuprofen) and modifier agent according to the present invention (where used, in the amounts shown in Table 2), are added to 0.05M HCl (50mL) and the resulting solution stirred for 15 minutes. After 15 minutes, a sample if taken for

analysis to determine the amount of ibuprofen dissolved in the HCl solution. Further dilution is conducted if required with a standard diluent (acetonitrile : water).

Experiment 3: Determination Of The Amount Of Ibuprofen Released From LDH-Ibuprofen Compositions By Addition Of Test Modifier Systems According To The Present Invention (Sodium Carbonate And Surfactant) To An LDH-Ibuprofen Material.

A composition containing 400 mg LDH-ibuprofen (200 mg dose of ibuprofen), sodium carbonate and a surfactant in different ratios where mixed together and added to 0.05M HCl (50mL) and the resulting solution stirred for 15 minutes. Samples of the of the reaction solution were removed and used to determine the amount of ibuprofen released by each of the sodium carbonate/surface active agent combinations using both the solvent system method and the solubility method described above. The results obtained are detailed in Figure 28.

Conclusion

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The results presented in Figure 28 highlight many interesting features of the relationship between a metal carbonate, and a surfactant, and the resulting effect this combination has on the % release of ibuprofen from an LDH matrix and the % solubility of the released ibuprofen in an acidic medium. Some of these features include:

The presence of sodium carbonate does not appear to provide any significant improvement on the % release of the active anion (41% v 40%), although the amount of released active anion which then dissolved in an acid medium is increased from 0.9% (when no sodium carbonate is present) to 25% (when 300mg sodium carbonate is present).

Neither the choice of surfactant nor the amount of surfactant (in the range 50mg to 300mg) appears to have any significant effect on the total amount of active anion released, this being in the range 59% to 77%. However, there is a wide variation in the solubility of the released active anion which suggests that not all of the surfactants act to solubilise the released active anion. Also the presence of sodium carbonate appears to act in a similar way with all surfactants because (apart for a couple of exceptions 200mg Sodium Lauryl Sulfate (SLS) and 200mg lecithin) the % release is of a similar order of magnitude for a given level of sodium carbonate.

The addition of <100mg sodium carbonate appears to cause a decrease in the % release, relative to the % release observed for 0mg sodium carbonate, whereas the addition of

>100mg sodium carbonate appears to increase % release and with 200mg sodium carbonate % release of 77 to 88% is observed.

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CLAIMS:

1. A composition comprising: i) one or more LDH-active anion materials comprising an LDH matrix intercalated with an active anion, and ii) a modifier system comprising a surfactant, in combination with sodium carbonate; wherein the active anion is ibuprofen and the composition has a weight ratio of the LDH matrix : sodium carbonate: the surfactant, of 1 : 1: 0.25 to 1, wherein the surfactant is selected from poloxamer, lecithin and SLS.

2. A composition according to claim 1 wherein the surfactant is present in a quantity of 50 to 200 mg, and further

comprising 400mg LDH-ibuprofen which contains 200mg ibuprofen and 200mg sodium carbonate.

3. A composition according to any preceding claim, wherein the surfactant is present in a quantity of 50, 100 or 200 mg

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4. A method for 1) controlling the total amount of an active anion released from an LDH matrix under acidic conditions designed to represent the conditions found in a fasted human stomach, and 2) increasing amount of released active anion which is dissolved in the acidic medium, the method comprising the step of forming a composition with the features of any of claims 1 to 3.

5. A formulation comprising a composition with the features of any of claims 1 to 3 in a form selected from dry granules, tablets, caplets, orally disintegrating tablets, orally disintegrating granules, lozenges, films, capsules, powders, effervescent formulations and buccal and sub-lingual formats.